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**Exhibit 1: Applicant statements and submissions for the record of the instant application**

Applicant respectfully requests leave to submit for the record additional information pertaining to the claims directed to hydrogen sulfide treatments. These claims have been rejected based on *Chemical Abstracts*, 115:56107 (1991), *Medline Abstracts*, Accession No. 92296647 (1992) *Embase Abstract*, Accession No. 2000083448 (2000), and *Toxcenter Abstract*, Accession No. 2002:618658 as allegedly teaching that hydrogen sulfide could not be administered to patients with pulmonary disorders (Office Action, page 4). Applicant notes that the cited abstracts correspond to full-text articles which have been provided herewith. In particular:

- *Chemical Abstracts*, 115:56107 (1991) corresponds to Jäppinen et al., 1990, *Br. J. Indust. Med.* 47:824-828 ("Jäppinen et al."; Ex. 2);
- *Medline Abstracts*, Accession No. 92296647 (1992) corresponds to Reiffenstein et al., 1992, *Ann. Rev. Pharmacol. Toxicol.* 109-134 ("Reiffenstein et al."; Ex. 3);
- *Embase Abstract*, Accession No. 2000083448 (2000) corresponds to Bhambhani, 1999, *Eviron. Epidem. Toxicol.* 1:217-230 ("Bhambhani"; Ex. 4); and
- *Toxcenter Abstract*, Accession No. 2002:618658 corresponds to *Environmental Heath Criteria: Hydrogen Sulfide*, World Health Organization, 1981 ("Environmental Heath Criteria"; Ex. 5).

In the full-text articles:

- Jäppinen et al. state "When asthmatic subjects were exposed in controlled conditions to 2 ppm of hydrogen sulfide for 30 minutes, no significant [adverse] changes in respiratory function occurred." (Ex. 1, p. 827);
- Jäppinen et al. state "[P]ractically no [deleterious] respiratory effects were noticed in our study, either among asthmatic subjects or among pulp mill workers, despite the irritant nature of hydrogen sulfide." (Ex. 1, p. 827);
- Reiffenstein et al. state "[I]n the asthmatic subjects [studied by Jäppinen et al.] there were nonsignificant increases in airway resistance (26.3%) and decreases in specific airway conductance (8.4%)." (Ex. 2, p. 119);
- Bhambhani states "The asthmatic subjects [studied by Jäppinen et al.] also did not experience any adverse effects in these respiratory function measurements as a result of hydrogen sulfide exposure." (Ex. 3, p. 221);
- Bhambhani states "[The asthmatic] group as a whole [studied by Jäppinen et al.] did not demonstrate any significant change in airway resistance and specific airway conductance." (Ex. 3, p. 221);
- Environmental Heath Criteria states that 100-150 ppm hydrogen sulfide is associated only with local eye and throat irritation in the canary, rat, guinea pig, and dog after many hours of exposure (Ex. 4, p. 29); and
- Environmental Heath Criteria states that 10.5 ppm hydrogen sulfide is the threshold for eye irritation after several hours of exposure (Ex. 4, pp. 11 and 40).

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# Exposure to hydrogen sulphide and respiratory function

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**Abstract**

**A study was carried out to assess possible effects of low concentrations of hydrogen sulphide on respiratory function. The cohort comprised 26 male pulp mill workers (mean age 40·3, range 22–60 years) with a daily exposure to hydrogen sulphide in the workplace, and 10 volunteers, who had asthma (three men, mean age 40·7, range 33 to 50 years, and seven women, mean age 44·1, range 31 to 61 years). The respiratory function of the pulp mill workers was monitored by measuring forced vital capacity (FVC), forced expiratory volume in one second ($FEV_1$), and bronchial responsiveness after at least one day off work and at the end of a workday. Bronchial responsiveness was tested by challenge with histamine. The 10 asthmatic subjects were exposed in laboratory conditions to 2 ppm of hydrogen sulphide for 30 minutes in an exposure chamber. Airway resistance (Raw) and specific airway conductance (SGaw) were assessed by a body plethysmograph, and the ventilatory capacities were measured with a flow volume spirometer. No significant changes in respiratory function or bronchial responsiveness related to exposure to hydrogen sulphide in the pulp mill workers were found. In the asthmatic subjects, Raw was increased by 26.3% and SGaw was decreased by 8·4% on average after exposure to hydrogen sulphide. These changes were not statistically significant. In two subjects, however, changes were greater than 30% in both Raw and SGaw, indicating bronchial obstruction. It is concluded that exposure for a relatively short time to hydrogen sulphide concentrations appreciably higher than those existing in ambient air do not cause noticeable effects on respiratory function.**

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Although sulphur dioxide is known to impair respiratory function,[1,2] few data exist about the effects of hydrogen sulphide in this respect. Hydrogen sulphide, however, is a potential hazard of the workplace in many areas, for instance, the pulp and oil industries. Hydrogen sulphide and other organic sulphur compounds such as methyl mercaptan are emitted from pulp mills into the ambient air, causing nuisance and health effects among the general population.[3] The adverse effects of high hydrogen sulphide concentrations exceeding the maximum workplace concentration of 10 ppm are known to some extent,[4] but there is a scarcity of information on possible respiratory or other effects caused by low hydrogen sulphide concentrations existing at workplaces or in ambient air around industrial sources.

We carried out a study to find out if low concentrations of hydrogen sulphide affect respiratory function. This was accomplished, firstly, by assessing the respiratory function of pulp mill workers exposed to low prevailing concentrations of hydrogen sulphide at their workplace and, secondly, by exposing voluntary subjects with bronchial asthma to a known low concentration of hydrogen sulphide under laboratory conditions.

## Subjects

### WORKERS EXPOSED TO HYDROGEN SULPHIDE

This group comprised 26 male pulp mill workers (mean age 40·3, range 22 to 60 years) with daily exposure to hydrogen sulphide usually below the maximum permitted concentration in the workplace of 10 ppm. The subjects were questioned by a nurse about their smoking habits (10 smokers) and previous allergies—namely, asthma, hay fever, atopic dermatitis (five cases). A skin prick test was performed on each subject using 12 common allergens to indicate possible atopic disposition (five atopic subjects).

ASTHMATIC SUBJECTS FOR EXPOSURE TO HYDROGEN SULPHIDE IN THE LABORATORY

The group consisted of 10 subjects, three men (mean age 40·7, range 33–50 years) and seven women (mean age 44·1, range 31–61 years). They had had bronchial asthma[5] for one to 13 years (mean 3·7 years) and had been using medication. Patients with severe asthma were not included in the study because a period of two days without taking drugs was recommended before the exposure to hydrogen sulphide. The stability of the asthma was assessed by monitoring PEF values twice daily at home with a peak flow meter (Spira, Respiratory Care Centre, Hämeenlinna, Finland) for at least one week before the study. The study design was accepted by the ethical committee of the hospital and consent was obtained from each subject.

## Methods

The spirograms of the pulp mill workers were obtained with a dry wedge spirometer (Vitalograph Ltd, England). In the laboratory exposure test, airway resistance (Raw), specific airway conductance (SGaw), and the flow volume loop were determined by a body plethysmograph (Gould, Holland). The measurements were accomplished in that order before exposure to hydrogen sulphide and 30 minutes after exposure. The values presented by Viljanen *et al*,[6] derived from a Finnish general population, were used as predicted normal values for forced expiratory volume in one second ($FEV_1$), forced vital capacity (FVC), Raw, and SGaw.

To test the bronchial responsiveness of the pulp mill workers, each subject was challenged twice; after a holiday or at least one day off from work, and at the end of a workday when there had been noticeable odour of hydrogen sulphide at the workplace. The histamine challenges were performed at the company health station near the workplace. The subjects were not exposed to accidentally high concentrations of hydrogen sulphide during the period of study (March 1987 to April 1989).

The histamine challenge test was performed by administering histamine diphosphate aerosol in ten tidal breaths with a No 40 de Vilbiss nebuliser (De Vilbiss Co, Somerset, PA), at increasing concentrations (0·1, 0·2, 0·4, 0·8, 1·6, and 3·2%), until a fall of 15% in $FEV_1$ was achieved or the maximum histamine diphosphate concentration of 3·2% was reached. Two selected nebulisers were in use, with an output of 0·092 and 0·115 ml aerosol per min at an airflow rate of 5 l per min. The threshold concentration was designated $PC_{15}$. The test was started with ten breaths from aerosol containing physiological sodium chloride. The two challenges were made at the same time of day to exclude possible confounding by diurnal variations in ventilatory function.

Possible differences between FVC, $FEV_1$, or $PC_{15}$ recorded in the two histamine challenge tests were assessed for all subjects and also for the following subgroups: (1) subjects exposed to measurable hydrogen sulphide concentrations (minimum 1 ppm); (2) those exposed workers who smoked; (3) those exposed workers who had previous allergies or bronchial asthma, and (4) the five atopic subjects with a positive reaction in the skin prick test.

The concentrations of hydrogen sulphide in the workplace were measured with an electrochemical continuous analyser (Sulfipac, Drägerwerk AG, Lübeck) by a trained hygienist just before the second histamine challenge test. The detection limit of the analyser was 1 ppm. The concentrations of hydrogen sulphide varied due to process conditions. Most measurements were between 2 and 7 ppm, with a range of 1 to 11 ppm. Even when the hydrogen sulphide concentration was below the detection limit of 1 ppm and thus not measurable with the analyser used, a definite odour of hydrogen sulphide was still present.

For the laboratory test, two asthmatic subjects were exposed simultaneously for 30 minutes to a hydrogen sulphide concentration of 2 ppm, which is one fifth of the Finnish maximum allowable workplace concentration of 10 ppm. The exposure was performed in a tile walled sealed exposure chamber with a volume of about 10 $m^3$. During controlled exposure, there was a constant oxygen flow of 2 l per min into the chamber, as well as a sufficient flow of hydrogen sulphide to maintain its concentration at 2 ppm. The concentration was monitored continuously with a sulphur dioxide analyser (Thermo Electron Instruments, model 43A) connected to a converter (Thermo Electron Instruments, model CDN-101) that transformed hydrogen sulphide into sulphur dioxide at 840°C. The analyser was calibrated according to the ISO/DIS standard 6249[7] with a permeation calibrator (Thermo Electron Instruments, model 360). The test gas, at a concentration of 10 ppm, was provided in laminated plastic bags by the research institute of Enso-Gutzeit Oy, and hydrogen sulphide was supplied to the chamber using a plastic tube.

For the histamine challenge test, the means and the standard errors of the means (SEMs) for the observations, and the differences between the means of observations in each group were calculated. The statistical significance of the possible differences was assessed using the *t* test for paired samples. For the hydrogen sulphide exposure test, the statistical significance of the possible differences between the first and second measurements was assessed using the *t* test for paired samples.

## Results

WORKERS EXPOSED TO HYDROGEN SULPHIDE

Among the exposed subjects as a whole (n = 26), no

*Table 1 Changes in respiratory function in subjects (n = 26) exposed to hydrogen sulphide at their workplace*

| Variable | Before exposure (B) Mean (SEM) | After exposure (A) Mean (SEM) | Difference (A–B) | p Value |
|---|---|---|---|---|
| FVC (l) | 4·94 (0·14) | 5·00 (0·14) | 0·06 | 0·42 |
| FVC (% predicted) | 94·4 (2·2) | 95·4 (2·3) | 1·0 | 0·39 |
| $FEV_1$ (l) | 4·10 (0·12) | 4·06 (0·12) | −0·04 | 0·27 |
| $FEV_1$ (% predicted) | 95·0 (2·1) | 94·1 (2·1) | −0·9 | 0·28 |

*Table 2 Changes in respiratory function in asthmatic subjects (n = 10) exposed to 2 ppm of hydrogen sulphide for thirty minutes*

| Variable | Before exposure (B) Mean (SEM) | After exposure (A) Mean (SEM) | Difference (A–B) | p Value |
|---|---|---|---|---|
| FVC (l) | 3·85 (0·29) | 3·85 (0·30) | 0 | 0·94 |
| FVC (% predicted) | 96·4 (5·1) | 96·1 (5·2) | −0·3 | 0·72 |
| $FEV_1$ (l) | 3·00 (0·23) | 2·99 (0·24) | 0·00 | 1·00 |
| $FEV_1$ (% predicted) | 89·9 (4·1) | 89·6 (3·9) | −0·3 | 0·80 |
| $FEF_{25-75}$ (l/s) | 2·58 (0·28) | 2·62 (0·31) | 0·03 | 0·75 |
| Raw ($kPa\,l^{-1}$) | 0·12 (0·01) | 0·14 (0·02) | 0·03 | 0·06 |
| Raw (% predicted) | 74·1 (9·2) | 93·2 (14·0) | 19·1 | 0·08 |
| SGaw ($kPa^{-1}\,s^{-1}$) | 3·97 (0·49) | 3·58 (0·52) | −0·40 | 0·17 |
| SGaw (% predicted) | 208·9 (25·5) | 188·0 (26·4) | −20·9 | 0·15 |

statistically significant changes in pulmonary function were found, assessed by FVC and $FEV_1$ (table 1), or in bronchial responsiveness, assessed by the histamine challenge test. In the first challenge, performed without exposure, $PC_{15}$ was more than 3·2% in 23 cases. In the other three cases, $PC_{15}$ was 2·8%, 3·0%, and 3·2%. In the second histamine challenge, performed after hydrogen sulphide exposure, $PC_{15}$ was more than 3·2% in 24 cases (1·6% and 2·8% in the others). The subject with $PC_{15}$ of 1·6% had dyspnoea and cough after the challenge and bronchial asthma was diagnosed subsequently.

When analyses were performed on the subjects with measurable (1 ppm or more) concentrations of hydrogen sulphide (n = 16), on smokers (n = 6), on workers with previous allergies (n = 4), and on atopic subjects (n = 5), no statistically significant changes in respiratory function were found.

ASTHMATIC SUBJECTS EXPOSED TO HYDROGEN SULPHIDE

All subjects experienced the odour of hydrogen sulphide as very unpleasant at the start of exposure, but rapidly became accustomed to it. The subjects also sensed nasal and pharyngeal dryness at the start. Three out of 10 subjects complained of headache after exposure.

There were no notable changes in the mean FVC, $FEV_1$, and forced expiratory flow ($FEF_{25-75\%}$) values after exposure to hydrogen sulphide in subjects with asthma (table 2). The Raw value was slightly decreased in two and increased in eight subjects, the range of the difference being from −5·95% to +137·78%. On average, there was an increase of 26·3% in Raw. The mean of Raw was increased by 25% after exposure (table 2), but this increase was not statistically significant and did not result in clinical symptoms.

The SGaw value was decreased in six and increased in four subjects. On average, a decrease of 8·4% in SGaw, with a range from −57·7% to +28·9% occurred (table 2), but the change was not statistically significant. When assessing the changes in Raw and SGaw, however, it should be noted that in two subjects there were changes of over 30% in both Raw and SGaw, indicating bronchial obstruction.

## Discussion

Although the effects of high concentrations of hydrogen sulphide on the body, including the respiratory system, are well known,[4] virtually no information exists about the effects of low concentrations. As it is practically impossible to arrange controlled experimentation on subjects using the low hydrogen sulphide concentrations usually found in ambient air, subjects in our study were exposed to a hydrogen sulphide concentration of 2 ppm. This concentration can be produced and measured fairly accurately, and is still only a fifth of the maximum permitted workplace concentration. Furthermore, it is close to concentrations usually found in well equipped kraft pulp mills without any accidental leaks.[8]

Other malodorous sulphur compounds are also found in kraft pulp mills and in their vicinity, so that exposure to pure hydrogen sulphide is virtually non-

existent. Concentrations of methyl mercaptan may be as high or even higher than those of hydrogen sulphide,[9] with dimethyl sulphide and dimethyl disulphide being found at a lower concentrations. The effects of these compounds on man are not adequately known, although the effects of all malodorous sulphur compounds at the cellular level are thought to be similar.

Relatively short term exposure at the workplace did not cause noticeable effects on respiratory function of pulp mill workers. The subjects sensed the odour, but rarely had other subjective symptoms. Testing bronchial responsiveness by inhaled histamine is a well known method with good reproducibility.[9 10] It should be noted, however, that it was not possible to assess the effects of long term exposure to hydrogen sulphide on respiratory function in this study. Furthermore, a healthy worker effect certainly exists and its magnitude cannot be estimated.

When asthmatic subjects were exposed in controlled conditions to 2 ppm of hydrogen sulphide for 30 minutes, no significant changes in respiratory function occurred. The airway resistance increased somewhat after exposure, but it was not reflected in the subjects' clinical condition. Hydrogen sulphide concentrations in the workplace can be momentarily much higher than 2 ppm, and it is not possible to predict on the basis of this laboratory study what kind of symptoms asthmatic subjects could have at higher concentrations.

Inhalation of noxious gases is a well recognised cause of exacerbation of asthma.[11 12] Sulphur dioxide, unlike ozone or nitrogen oxide, has a bronchoconstrictive effect of a dose dependent type, at least when inhaled during exercise.[11] Sulphur dioxide and ozone increase bronchial responsiveness in both asthmatic and non-asthmatic subjects in laboratory conditions.[13 14] These gases are of a strongly irritant nature, which suggests that the increased airway responsiveness may be a consequence of an acute inflammatory response.[11 15]

Malodorous sulphur compounds existing in ambient air have been shown to cause mucosal and conjunctival irritation even at low concentrations,[3] and thus somewhat stronger respiratory effects were expected to occur in this study than were found. Hydrogen sulphide dissociates at neutral pH to a hydrogen sulphide anion, which is a strong base and thus causes mucosal irritation.[4] The main effect of hydrogen sulphide on the cellular level is inhibition of the enzyme cytochrome oxidase at the end of the mitochondrial respiratory chain.[16] This inhibition of the energy metabolism—probably affecting mucosal nerve endings—may explain why practically no respiratory effects were noticed in our study, either among asthmatic subjects or among pulp mill workers, despite the irritant nature of hydrogen sulphide.

Because natural gas, with a very low sulphur content, is used as the energy source by the local industry, sulphur dioxide concentrations in the ambient air of South Karelia are low; in Imatra, in the vicinity of the pulp mills, 24 hour average sulphur dioxide concentrations have been under 30 $\mu g/m^3$.[17] It is unlikely, therefore, that exposure to sulphur dioxide in ambient air has affected the findings.

In our study, an exposure for a relatively short time to hydrogen sulphide concentrations at least 10 times higher than those usually found in the ambient air caused only minor respiratory effects among asthmatic subjects. In two out of 10 subjects, however, there were changes of over 30% in both Raw and SGaw as a sign of bronchial obstruction. It was also found that hydrogen sulphide concentrations in the workplace lower than the threshold limit value of 10 ppm do not cause noticeable respiratory effects in non-asthmatic workers. As the material was limited, the results of our study should be considered as preliminary and further studies are warranted. To our knowledge, this is the first study of the effects of hydrogen sulphide on respiratory function utilising exposure to the gas in the laboratory.

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# Correspondence and editorials

The *British Journal of Industrial Medicine* welcomes correspondence relating to any of the material appearing in the journal. Results from preliminary or small scale studies may also be published in the correspondence column if this seems appropriate. Letters should be not more than 500 words in length and contain a minimum of references. Tables and figures should be kept to an absolute minimum. Letters are accepted on the understanding that they may be subject to editorial revision and shortening.

The journal now also publishes editorials which are normally specially commissioned. The Editor welcomes suggestions regarding suitable topics; those wishing to submit an editorial, however, should do so only after discussion with the Editor.

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# TOXICOLOGY OF HYDROGEN SULFIDE

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## INTRODUCTION

### *Historical Background*

It is almost 300 years since the first description of hydrogen sulfide ($H_2S$) toxicity (1). There have, however, been few reviews and only one research conference (2) on $H_2S$ toxicity. Numerous governmental agencies concerned with occupational health or the environment have at various times prepared documents related to regulation of $H_2S$ exposure (e.g. 3, 4).

An excellent history of the early experience with $H_2S$ appeared in the recent conference proceedings (5). A review in 1984 (6) included a bibliography of almost 1300 references, 196 of which were cited in the text. The general opinion was that sulfide inhibited oxidative enzymes in a manner similar to



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cyanide, particularly enzymes involved with oxidative phosphorylation, but it must be concluded that additional processes are operating. Therapeutic measures have been suggested that follow the pattern used for the treatment of cyanide poisoning. However, animal experiments have not proved their validity for postexposure therapy, and clinical reports are still scarce. Recent advances have been made in the diagnosis of $H_2S$ poisoning, teratogenicity, and neurological and respiratory effects and have opened new possibilities for therapy.

$H_2S$ poisoning is still a problem because of widespread environmental and occupational exposure from industrial activities, e.g. paper pulp mills, heavy-water production, urban sewers, and farming, to name but a few of the more than 70 identified commercial sources. $H_2S$ is the predominant sulfur contaminant of natural gas and ranges in concentration from <1 to >90%. At least three epidemiological studies have recently addressed the health of populations exposed to this toxic gas (7–9).

## *Physicochemical Properties*

$H_2S$ is a colorless gas heavier than air ($d = 1.19$) with a molecular weight of 34.08 (10). It is the sulfur analog of water. It can be oxidized by a variety of agents to form sulfur dioxide ($SO_2$), sulfates such as sulfuric acid, and elemental sulfur (these products also have toxicological implications). One gram of $H_2S$ will dissolve in 242 ml of $H_2O$, 94.3 ml of absolute ethanol, or 48.5 ml of diethyl ether at 20°C. Because of its lipid solubility, it easily penetrates biological membranes. $H_2S$ evaporates from aqueous solutions (vapor pressure = $18.75 \times 10^5$ Pa). An aqueous solution will dissociate (see Equation 1), yielding a hydrosulfide anion and sulfide ion; the two pKa values are 7.04 and 11.96, respectively. At a physiological pH of 7.4, approximately one-third of $H_2S$ exists as the undissociated form and two-thirds as the hydrosulfide anion.

Some useful conversion factors for $H_2S$ are as follows: 1% volume = 10,000 ppm, 1 mg liter$^{-1}$ = 717 ppm (STP), and 1 ppm = 1.4 mg m$^{-3}$.

$$H_2S \rightleftarrows H^+ + HS^- \rightleftarrows 2H^+ + S^{2-} \qquad 1.$$

## *Species Comparison*

The effects of acute and chronic exposure to $H_2S$ in many vertebrates and invertebrates have been investigated from three different points of view: lethality, on commercially valuable species, and mechanism of adaptation. The reader is directed to reviews on this subject (4, 6, 11, 12). Briefly, lethality data for humans, dogs, cows, goats, monkeys, mice, guinea pigs, and rats are very similar, probably because the effect of $H_2S$ on eukaryotic cells is similar (see ref. 11 for a discussion). Table 1 shows the effects of $H_2S$

**Table 1** Human physiologic responses to exposure to hydrogen sulfide[a]

| Concentration of $H_2S$ ppm | mg $m^{-3}$ | Physiological responses |
|---|---|---|
| 0.003–0.02 | 0.0042–0.028 | Odor threshold |
| 3–10 | 4–14 | Obvious unpleasant odor |
| 20–30 | 28–42 | Strong offensive odor ("rotten eggs") |
| 30 | 42 | Sickening sweet odor |
| 50 | 70 | Conjunctival irritation |
| 50–100 | 70–140 | Irritation of respiratory tract |
| 100–200 | 140–280 | Loss of smell (olfactory fatigue)[b] |
| 150–200 | 210–280 | Olfactory paralysis[b] |
| 250–500 | 350–700 | Pulmonary edema |
| 500 | 700 | Anxiety, headache, ataxia, dizziness, stimulation of respiration, amnesia, unconsciousness ("knockdown") |
| 500–1000 | 700–1400 | Respiratory paralysis leading to death, immediate collapse, neural paralysis, cardiac arrhythmias, death |

[a]Adapted from Beauchamp et al (6) and other sources (2, 4, 108).
[b]Data require reevaluation because they are based on recollection of "knockdown" victims, who are known to have memory deficits (5).

on humans. There are some anomalies in the reported findings. Guinea pigs, but not rats, were reputed to die from exposure to 100 ppm of $H_2S$. This may be related to the fact that guinea pigs have a more extensive nasal labyrinth, are obligate nose breathers, and did not evolve in a high-$H_2S$ atmosphere (sewers) like rats did (see 5). In obligate nose breathers, cellular damage, exfoliation, and mucus secretion cause the nasal passages to plug up, and the animals simply cannot breathe and hence die from lack of oxygen. This effect has been seen in comparisons of nose-breathing and tracheotomized guinea pigs exposed to cigarette smoke (W. C. Hulbert, unpublished data).

Birds (canaries) are more sensitive than mammals to $H_2S$: 100 ppm causes 100% mortality. It is unknown whether the mechanism is similar to that in guinea pigs or whether it is due to altered metabolic or neurological function.

Extensive studies of the effects of $H_2S$ on aquatic vertebrates have been conducted (see ref. 14 for a review), particularly channel catfish, brown trout, walleye, northern pike, blue gill, rainbow trout, and the white sucker. $H_2S$ affects these species at all stages of development from eggs to adults, and many effects seem related to the ability of the species to express tolerance or adaptation (15). Fish reared in sublethal concentrations of $H_2S$ exhibited growth enhanced by 50 to 200% (14, 16), owing to fungicidal and bactericidal effects of $H_2S$, similar to the effects of antibiotics normally used with captive fish. However, it was also noted that the fish were significantly less active (16) and showed signs of respiratory distress. Histological analysis of the gill lamellae revealed structural alterations of the gill filaments, which were

shortened and thickened, indicating chronic irritation. Unfortunately, there have been no analyses of muscle and fat content, muscle contractility or enzyme levels, or effects of exercise, factors that may be more significant than the simple enhancement of growth. $H_2S$ becomes a major problem in fish aquaculture during harvesting (17): when anaerobic sediments of fish ponds are disturbed during netting, $H_2S$ levels throughout the water column are elevated to the toxic range.

Sulfide is abundant in the marine environment (especially near volcanic vents), and many vertebrate and invertebrate species (e.g. crabs, clams, and tubeworms) have evolved strategies for dealing with its presence. These include sulfide detoxification in the body wall, binding and oxidation of sulfide by blood components and by cytosolic factors, oxidation by mitochondria, sulfide-insensitive cytochrome *c* oxidase, and ATP production from sulfide oxidation (see ref. 18 for a review).

### *Target Organ Systems*

Most organ systems are susceptible to the effects of $H_2S$; therefore, this toxic gas has often been regarded as a broad-spectrum toxicant. The biological responses to $H_2S$ are dependent on the organ system; each system exhibits a different threshold responsiveness, perhaps as a function of concentration, time, or rate of exposure (19). Tissues most susceptible to $H_2S$ toxicity are those with exposed mucous membranes and those with high oxygen demands. The effects of prolonged exposure to low concentrations are not well documented. It has been proposed that the toxicity may be cumulative (20) or noncumulative (21) and that the effects can be completely reversible. Recovery from acute intoxication is usually rapid and complete, depending upon exposure; however, some symptoms may persist (9) and some aftereffects may be irreversible as a result of secondary effects caused by lack of oxygen due to respiratory paralysis and/or pulmonary edema (7, 21).

## NERVOUS SYSTEM

Acute exposure to $H_2S$ leads to sudden fatigue, vertigo, intense anxiety, convulsions, unconsciousness, and respiratory failure. After resuscitation, victims may suffer coordination and psychiatric disturbances, including hallucinations and amnesia. Chronic exposure leads to a variety of physiological and psychological effects (see Table 2). Early neurological studies concerned the increase in respiratory rate seen in moderate $H_2S$ exposures; this increase was attributed to stimulation of peripheral chemoreceptors (6). However, little progress had been made in describing the neurological sequelae of high $H_2S$ exposure until the advent of current electrophysiological techniques.

### *Brain Sulfide Content in Poisoning*

The sulfide ($S^{2-}$) concentration present in tissues following poisoning was unknown until recently. A recently developed, extremely *sensitive* (2 $\mu$g liter$^{-1}$) method (22, 23), specific to $S^{2-}$ and ideal for analysis of tissue, has defined the appropriate concentration of $H_2S$ or its salts for experimental use in the brain. The method is 50-fold more sensitive than earlier methods (24). Surprisingly, both rats and humans have a relatively high endogenous level of $S^{2-}$: 1.57 $\mu$g g$^{-1}$ for whole brain and 0.67 $\mu$g g$^{-1}$ in the midbrain. It would be of interest to know the $S^{2-}$ levels in brains of ruminants, since they produce large quantities of $H_2S$. Recently bovine brain levels of $S^{2-}$ were reported to be about 5.3 $\mu$g g$^{-1}$ (24a), although it is not known how the HPLC method used compares with the method used for rats and humans (22, 23). At the 50% lethal dose ($LD_{50}$) of NaHS (15 mg kg$^{-1}$) the level of $S^{2-}$ in rat brain was approximately 3.1 $\mu$g g$^{-1}$ ($\approx$75 $\mu$M). By contrast, another recent method for tissue $S^{2-}$ analysis (25, 26) gave much lower concentrations in the brain. Significant to its effect on respiration, sulfide is selectively taken up by brain stem compared with other brain areas (27). Inhalation of 1600 ppm of $H_2S$ and intraperitoneal (i.p.) injection of 30 mg of NaHS kg$^{-1}$ ($LD_{100}$ doses within 4 min) produced indistinguishable increases in $S^{2-}$ levels in the brain (28).

### *Brain Neurotransmitter Content*

Because of their essential role in central nervous system (CNS) function, the content and release of neurotransmitters during acute and chronic exposure to $H_2S$ or sulfide salts have been determined. Acute i.p. treatment with NaHS ($2\times LD_{50}$) increased the concentrations of alanine, aspartate, $\gamma$-aminobutyrate (GABA), glutamate, glutamine, glycine, and taurine selectively in the brain stem; minor or no changes were seen in other brain areas (29). This dose also increased serotonin (5-HT), dopamine, epinephrine, and norepinephrine levels in the brain stem, the only region where all four amine levels changed (30). These changes in catecholamine and 5-HT levels are due to inhibition of monoamine oxidase (MAO). Acute treatment with sulfide also inhibits acetylcholinesterase (31) and $Na^+/K^+$ATPase (see Electrophysiological Effects). Reversal of MAO inhibition was achieved ex vivo by removal of bound sulfide with the persulfide reagent dithiothreitol (32).

Experimental handling of rats produced increases in brain stem glutamate, glutamine, and taurine levels. Subacute treatment with NaHS (0.5x $LD_{50}$) resulted in a reduction of this stress-induced increase (33). This dose of NaHS had no effect on amino acid levels in brain stems of mice (34). Chronic exposure depressed brain amino acid transmitters (see Reproduction and Development). Therefore, it appears that degradation of amino acids (and

amines) is inhibited by acute exposure, but that synthesis is also inhibited by chronic exposure.

## *Neurotransmitter Release*

Release of amino acids has been studied by push–pull perfusion (35) because of evidence that NaHS depresses synaptic transmission presynaptically (36–39). Two paradigms were used: (*a*) NaHS ($LD_{50}$) was given i.p. or (*b*) 3–4 $\mu$g of NaHS $ml^{-1}$ (the concentration of $S^{2-}$ in the brain after administration of $LD_{50}$) was included in the perfusion medium. Perfusates from surviving animals revealed that most changes in amino acid release in the hippocampus or caudate-putamen were immediate or delayed increases (40, 41). However, in the brain stem reticular nucleus, the only change was a delayed decrease in glycine release (42). These results do not provide evidence that sulfide inhibits transmission by depressing transmitter release.

## *Electrophysiological Effects*

Many in vitro neuronal preparations have been used as models in the study of the actions of sulfide, including those discussed below. Ideally, studies of respiratory rhythm generator cells would be desirable, but the technical difficulties of intracellular recording from a sufficient number of these neurons has led to the use of dorsal raphe as a typical midbrain nucleus. The use of the rat hippocampus may relate to the memory losses that are common in survivors of sulfide poisonings.

FROG SYMPATHETIC GANGLION In view of the changes in catecholamine levels and in acetylcholinesterase activity (31) after administration of sulfide, effects of NaHS in the frog sympathetic ganglion have been investigated by the sucrose gap method (43, 44). With this technique, $\alpha_2$-epinephrine, muscarinic and nicotinic receptors, and $Na^+/K^+$ATPase electrogenic pump activity can be studied (45, 46). NaHS reversibly depolarized the ganglion, but did not alter the depolarizing effect of nicotine. However, the hyperpolarizing effects of epinephrine and muscarine were both reversibly increased by NaHS. The hyperpolarizing response to pump activation did not change while NaHS was present, but was greatly potentiated after removal of the NaHS, recovering to normal after 45 min. A similar effect occurred in mammalian neurons (see Hippocampal CA1 Neurons, below). It is remarkable that these neurons were exposed to sulfide for extended periods without being irreversibly damaged.

It is tempting to suggest that the sulfide-induced depolarization is due to inhibition of the electrogenic pump, either directly or from inhibition of ATP production; however, this seems unlikely since $Na^+/K^+$ATPAse activity in the presence of sulfide was equal to that in the control.

CRAYFISH SENSORY NEURON This preparation *(Procambarus clarkii)* was used to study the effect of sulfide on action potential (AP) generation and conduction, by using extracellular recording (47, 48). Sulfide salts ($<10^{-4}$ M) caused an initial brief ($\approx$1 min) block of APs, then a prolonged enhancement of AP amplitude, and then another brief inhibition of APs upon washout. Higher concentrations of sulfide caused irreversible changes. In the absence of intracellular studies, the reason for these changes remains to be elucidated. Sulfide did not, however, alter the rate of AP conduction. This is similar to earlier results obtained with frog sciatic nerve, for which large concentrations (1–100 mM) of sulfide only slightly reduced the conduction velocity (49).

MOUSE NEUROBLASTOMA CELLS Murine neuroblastoma cells, clone N1E-115 derived from sympathetic ganglia, were used to study tetrodotoxin (TTX)-sensitive $Na^+$ channels by the patch–clamp method (50). $Ca^{2+}$ and $K^+$ currents were blocked by $Cd^+$, $Cs^+$ and tetraethylammonium ($TEA^+$). NaHS, even as high as 10 mM, completely failed to alter the TTX-sensitive $Na^+$ channels. As controls for sulfur-containing compounds, trials were also done with taurine and cysteic acid, neither of which alone affected the $Na^+$ channels. It was discovered, however, that the combination of NaHS and either amino acid completely and reversibly inhibited the channels. Other sulfur-containing reagents (0.8 mM $\beta$-mercaptoethanol and 2 mM dithiothreitol) inhibited $Na^+$ channels by themselves. In in vitro situations it seems unlikely that sulfide will affect APs. However, in vivo, where free taurine levels are normally high and further increased by sulfide, taurine could play a role in $H_2S$ depression of CNS function.

HIPPOCAMPAL CA1 NEURONS CA1 neurons in hippocampal slices have been studied in current clamp by using potassium acetate–containing intracellular electrodes (36–38; R. J. Baldelli, R. J. Reiffenstein & W. F. Colmers, unpublished data). Slices were treated with 27–200 $\mu$M NaHS. The amplitude, duration, and threshold voltage of APs in CA1 neurons were unaffected by 80 $\mu$M NaHS. The initial response of these neurons to NaHS was a rapid, reversible, concentration-dependent hyperpolarization (IH) and reduction of input resistance. Both effects were maximal at 160 $\mu$M NaHS. The reversal potential for the conductance change was $-100$ mV, or slightly less than the calculated $E_K$ for these cells. An even more striking effect of NaHS was a further hyperpolarization (WOH) that occurred immediately after washout of the NaHS. This also was concentration dependent, being maximal at $>200$ $\mu$M. Synaptic transmission, measured by extracellularly recorded

population spike and EPSP field potentials, and by intracellular EPSPs, was depressed by NaHS.

Pharmacological investigation of the IH and the WOH suggests that these are due to the opening of a $K^+$ channel and to activation of $Na^+/K^+$ ATPase, respectively. Maximal responses to 200 $\mu$M NaHS were studied (36–38; R. J. Baldelli, R. J. Reiffenstein & W. F. Colmers, unpublished data). Extracellular application of 1 $\mu$M TTX (to block evoked transmitter release), 1 mM 4-aminopyridine (4-AP) to block the somatic "A" and "D" $K^+$ currents, or 30 $\mu$M muscarine to block the voltage-dependent "M" current, did not alter the IH. However, it was reduced by 50 mM (but not 10 mM) $TEA^+$ (36–38) and by 2 mM $Cs^+$. Extracellular $Ba^{2+}$ (1 mM), extracellular $Ba^{2+}$ plus $Cs^+$, and intracellular $Cs^+$ blocked the IH and unmasked a depolarization response to NaHS. Conductance changes were significantly reduced only by $Ba^{2+}$ or intracellular $Cs^+$ (36; R. J. Baldelli, R. J. Reiffenstein & W. F. Colmers, unpublished data). Intracellular release of neither MgATP nor $Cl^-$ reduced the IH and change in conductance.

Thus, it seems reasonable that the IH is due to increased conductance of a $K^+$ channel. Comparison of the data with two recent compendia of $K^+$ channels and their inhibitors (52, 53) makes it relatively easy to determine what that channel is not. It does not involve the fast transient voltage-dependent $I_A$, nor $I_D$, nor the $Ca^{2+}$-activated nonspecific cation channel ($I_t$), since 4-AP was ineffective, nor $I_M$, as muscarine did not inhibit it but $Cs^+$ did. Because sulfide blocks oxidative phosphorylation (6), the consequent depletion of ATP could activate ATP-sensitive $K^+$ conductances, but injection of ATP did not alter the IH. The conclusion that a $gK_{ATP}$ is not involved must be tempered as the mechanism of $K^+$-channel control by ATP is not understood; this action of ATP may also be inhibited, given the number of enzymes known or inferred to be inhibited by sulfide. $TEA^+$ blocks many $K^+$ currents, including voltage-dependent "delayed rectifiers" and some $Ca^{2+}$-activated $K^+$ channels (52). The cardiac-type inward rectifier ($I_{IR}$) fits the antagonism data (inhibition by $TEA^+$, $Cs^+$, and $Ba^{2+}$, but not by 4-AP).

None of the procedures listed above, except intracellular $Cs^+$, inhibit the WOH (36–38; R. J. Baldelli, R. J. Reiffenstein & W. F. Colmers, unpublished data). Moreover, the NaHS-induced $K^+$ conductance changes often recovered before the maximum WOH was reached. The $Na^+/K^+$ATPase inhibitor strophanthidin (3–30 $\mu$M) did inhibit the WOH; however, this treatment depolarized the neurons, and NaHS caused further depolarization. Thus it is likely that the WOH results from activation of $Na^+/K^+$ATPase, just as in the frog sympathetic ganglion. The NaHS-induced depolarization seen in the presence of strophanthidin suggests that sulfide does inhibit $Na^+/K^+$ATPase in this preparation, although this is not so clear when using frog ganglia.

Neither did the treatments listed above affect the depression of synaptic transmission (36–38), which suggests a presynaptic effect. However, this is not consistent with the release experiments, evidence that depolarization by iontophoresed glutamate pulses can be inhibited (36), or inhibition of glutamate binding to hippocampal neuronal membranes (K. Fung, M. W. Warenycia, S. B. Kombian & R. J. Reiffenstein, unpublished data), all of which suggest a postsynaptic effect.

DORSAL RAPHE NEURONS Effects of NaHS similar to those obtained in hippocampal CA1 cells have also been observed in voltage-clamped serotonergic (55) dorsal raphe neurons (39). Some cells responded to NaHS with an IH (outward current) followed by a WOH, as in CA1 neurons. However, in some of these raphe neurons the IH was superimposed on a sulfide-induced depolarization (inward current). In both cases, blockade of the IH with $Ba^{2+}$ plus $Cs^+$ revealed an underlying inward current. Some neurons responded only with initial inward currents, followed by the same WOH. In all cases the WOH was blocked by strophanthidin. The NaHS-induced inward currents were also occluded by the strophanthidin, showing that the depolarization was due to at least partial inhibition of $Na^+/K^+$ATPase by sulfide. A few neurons appeared to be unresponsive to sulfide.

Although the mechanism of action of $H_2S$ on neurons is not completely clear, sulfide can activate $K^+$ conductances in at least two very different kinds of neurons, and these conductances are sensitive to extracellular application of $Ba^{2+}$ and $Cs^+$. Upon blockade of these $K^+$ currents, all neurons showed a depolarizing response to NaHS, which is caused by a voltage-independent (at least in dorsal raphe neurons) inward current and which may well be due to suppression of outward current generated by the $Na^+$-$K^+$ exchanger. Dorsal raphe neurons are variably affected by sulfide, perhaps reflecting the relative contributions of the $Na^+/K^+$ATPase activity and the $Cs^+$-$Ba^{2+}$-sensitive $K^+$ conductances in their resting state. All cells that responded to NaHS also showed the outward current response to washout of NaHS. This action of sulfide on $Na^+/K^+$ATPase in mammalian CNS neurons is rapidly and completely reversible. Clearly, other types of neurons will have to be sampled before a generalization about neural mechanisms of sulfide toxicity can be made. At present, the relatively uniform responses of hippocampal CA1 neurons do suggest that inhibition may be the reason for temporary memory deficits which occur in high $H_sS$ exposure. The WOH, and potentiation of other inhibitory mechanisms, may well slow the return of function.

HYPOXIA AND ANOXIA Are the effects of $H_2S$ on nervous tissue simply those due to inhibition of oxidative metabolism? Similar membrane potential responses to those induced by sulfide have been shown in vitro during anoxic

or hypoxic conditions (56–60), but there seem to be pharmacological dissimilarities. The anoxia-induced IH in hippocampal pyramidal neurons was reported to be blocked by 4-AP (0.4 mM) (56). Another group (57) found that $Ba^{2+}$ (0.5 mM) blocked the IH but that 4-AP (0.2–1.5 mM) and $Cs^+$ (2–4 mM) were ineffective (57, 58). Neither group found $TEA^+$ (3–10 mM) effective; however, less than 50 mM $TEA^+$ was ineffective against NaHS (36). It has been variously concluded that the anoxia-induced IH is in part due to a $Ca^{2+}$-sensitive gK (59) and also due to a muscarine- or carbachol-sensitive $gK$ ($I_M$) (60). None of these anoxia data are consistent with the sulfide pharmacology. A reoxygenation hyperpolarization similar to the sulfide WOH has also been observed (57, 58). This also seems to be due to the electrogenic pump, since it was abolished by low $K^+$ concentrations or 1 $\mu$M ouabain. The action of sulfide is often compared to that of cyanide (6), which does block oxidative metabolism; however, on the basis of comparison of the actions of cyanide and sulfide on frog nerve (49), it has been concluded that sulfide acts by other than metabolic actions. At this time it seems that the processes caused by sulfide and simple anoxia, although producing a similar end point, are not completely identical. In view of the controversy over the actions of cyanide and sulfide and the role of chemically-induced "anoxia," it would appear essential to test the actions of cyanide in a similar manner.

## RESPIRATORY SYSTEM

The effects of toxic gas exposure on the respiratory system have been the focus of intensive investigations (see ref. 61 for a review). One of the hallmarks has been the change in bronchial reactivity to inhaled nonspecific agonists. Although the patterns vary, at some level of exposure there is an increase in bronchial reactivity or hypersensitivity and the expression of asthmalike responses. However, there are few animal studies and even fewer human studies that have examined this very important effect on the pulmonary system.

### *Clinical Manifestations*

In reviewing the case studies of accidental exposure, the respiratory complaints are the second major group of symptoms reported after neurological ones. The most prevalent respiratory symptom following accidental exposure to $H_2S$ is dyspnea (7). In fact, dyspnea accounted for symptom complaints in 23% of 250 $H_2S$-exposed workers who filed claims with the Workers' Health and Safety Compensation Board in Alberta, Canada. Other prevalent symptomatic complaints in that study were sore throats, coughs, and chest pain. In nine of these workers given pulmonary function tests, three showed an obstructive pattern. Other respiratory signs and symptoms seen less frequently

were pulmonary edema, cyanosis, and hemoptysis. One of the complications following exposure to $H_2S$ is the development of pneumonia, which may be related to the inhibitory effect of $H_2S$ on alveolar macrophages and their subsequent ability to inactivate bacteria (62).

Only one study has evaluated the effects of environmental levels of $H_2S$ on pulmonary function (8). This was an examination of the effects of living downwind from a natural-gas refinery. Although the investigations did not assess hypersensitivity by challenge with either $H_2S$ or a nonspecific agonist such as methacholine, they did show that there was an excess of respiratory symptoms in the exposed area, especially in children from 5 to 13 years of age and in never-smokers over 14 years of age. Unfortunately, their study did not assess the direct effects of $H_2S$, but, rather, those of the combined emissions from the gas refinery.

A recent study (63) evaluated the effects of inhaling $H_2S$, 2 ppm for 30 min, on pulmonary function in a cohort of pulp mill workers who either were asymptomatic for asthma or had symptoms of asthma. No effect on airway resistance or specific airway conductance in the asymptomatic workers was found. In the asthmatic subjects there were nonsignificant increases in airways resistance (26.3%) and decreases in specific airway conductance (8.4%). The investigators concluded that exposure for a relatively short time to $H_2S$ concentrations appreciably higher than those existing in ambient air in the pulp mill does not cause noticeable effects on respiratory function; however, in 2 of the 10 asthmatic subjects, changes greater than 30% in both resistance and conductance were found, indicating airflow obstruction.

These results must be evaluated in light of two factors. First, no non–pulp mill workers were included in the study. Second, as it is known that a self selection takes place in workers in the pulp and paper industry, such that only those who can tolerate the fumes work in the environment (64), this may significantly pre-bias any results.

It is significant that symptoms of obstructive air flow only occurred in the asthmatics. One might speculate that in a more normal population, there may be more responses to the inhalation of $H_2S$ in asthmatic subjects, consistent with their hypersensitivity to toxic gases. To date, there have been no pulmonary function studies evaluating a cross-section of the general population to exposure to $H_2S$. Until that is done, the effects of $H_2S$ on pulmonary function and bronchial reactivity in humans will remain speculative.

## *Animal Studies*

There have been two major animal studies that have examined the acute and subchronic effects of inhaling $H_2S$ on pulmonary function, bronchial reactivity, and lung histology (65–70). The subchronic experiments were designed to

assess the applicability of the current occupational standards for exposure to $H_2S$ in the workplace. Currently proposed regulations (71) for exposure of workers to $H_2S$ are a time-weighted average-threshold limit value (TWA-TLV®) of 10 ppm for a week consisting of five 8-hr days and a time-weighted average short-term exposure limit (TWA-STEL®) of 15 ppm for 15 min. These levels were initially intended to prevent eye injuries (11), but the standards were never tested in animals to determine whether they protected against pulmonary injury.

SUBCHRONIC LOW-LEVEL INHALATION Subchronic studies (65, 66, 68–70) showed that the exposure to $H_2S$ at 1, 10 and 100 ppm for 8 hr per day for 5 weeks had no effect on baseline measurements of airways resistance ($R_L$, a measure of central airway function), dynamic compliance ($C_{dyn}$, a measure of peripheral airway function), tidal volume, minute volume, or heart rate. It was also found that the maximal changes in $R_L$ and $C_{dyn}$ with an aerosol methacholine (MCh) challenge were comparable for all groups. This was unexpected in view of reported damage to the nasal mucosal epithelium following $H_2S$ exposure (72). It was anticipated that baseline measurements would be elevated, reflecting changes in airway caliber due to injury.

Although baseline and maximal responses to MCh were unchanged, there was a leftward shift in the $R_L$ and $C_{dyn}$ dose-response curves (DRC) for some rats: these responded maximally to a 10-fold-lower MCh dose at all $H_2S$ exposure levels. Sensitivity (concentration of agonist causing a half-maximal response) and reactivity (rate of the response) varied widely; however, cluster analysis did show distinct groupings of response, with clear separation between animals responding like the controls and hyperreactive individuals (70).

Histologic examination of the trachea and lungs in normal and hyperreactive rats revealed only subtle differences in structure; neither an inflammatory infiltrate nor increased numbers of mast cells were seen in the hyperreactive animals. In many rats exposed to $H_2S$, there were two consistent dose-related peculiarities: proliferation of the ciliated cells in the tracheal and bronchiolar epithelium, and a lymphocyte infiltrate of the bronchial submucosa in addition to the recognized bronchoalveolar lymphatic tissues. Neither change has been reported to be causally related to bronchial reactivity.

The mechanism of the hyperreactivity may be related to increased airway mucosal permeability. Low concentrations of thiols such as $H_2S$ and $CH_3SH$ are known to markedly increase permeation of macromolecules across the porcine oral mucosa (73). A series of studies on the acute effects of cigarette smoke inhalation have shown that increased bronchial reactivity is associated with increased mucosal permeability (74).

The identification of individual rats that were hypersensitive after inhaling

$H_2S$ has significance for accidental human exposure to $H_2S$ and possibly to other toxic gases. In some rats the hyperreactive response occurred after they had inhaled only 1 ppm, which is only twice the concentration recorded in the city of Edmonton, Canada, during the 1982 gas well blowout 138 km distant. Whether prolonging the exposure would recruit more individuals into the hyperreactive subgroup is not known, but the DRC seems to imply this. These findings indicate that the occupational exposure standards that were established upon other criteria (eye damage) may not necessarily protect the pulmonary system from damage.

ACUTE HIGH-LEVEL INHALATION The acute effects on pulmonary function and bronchial reactivity of inhaling moderately high concentrations of $H_2S$ for 1 h were investigated by using guinea pigs (67, 68). There were no effects on baseline $R_L$ or $C_{dyn}$ for the control, 100-ppm, and 500-ppm groups, but there was a leftward shift in the aerosol MCh DRC that was related to the $H_2S$ dose. Sensitivity and reactivity increased 10- and 3-fold, respectively, for $R_L$ and 3- and 4-fold, respectively, for $C_{dyn}$. Thus, the central and peripheral airways of the animals were more sensitive to inhaled MCh, and the slope of the DRC was steeper after exposure to $H_2S$. There are several possible explanations. Because baseline measurements were not significantly different, it is doubtful that the starting airway caliber is involved. Increased mucosal permeability is possible, and its relationship with hyperreactivity is well documented, as discussed above. Another possible mechanism is a change in the smooth muscle itself. Alterations in the sensitivity of the irritant receptors are also possible although not likely, given the lack of effects of $H_2S$ on APs and nerve conduction (see Electrophysiological Effects).

The hypothesis that the increased sensitivity and reactivity were due to increased mucosal permeability has been tested (75). First, following exposure to 100 and 500 ppm of $H_2S$, the mucosa became hyperpermeable to dextran (FITC-T-40; molecular weight, 40,000) in a dose-related way. Transmission electron-microscopic analysis showed precipitation of the dextran in the intercellular spaces in airway tissues from the animals that had been exposed to $H_2S$ but not the controls, corroborating the physiological measurements on dextran in blood. Second, when MCh was injected intravenously (i.v.) (bypassing the effect of the airway mucosa by delivering the MCh directly to the smooth muscle), it was found that there was no difference in the DRCs between any of the control or $H_2S$-exposed animals. This confirmed that bronchial hyperactivity following the acute exposure to $H_2S$ involved hyperpermeability of the airway mucosa, which facilitates the access by inhaled agonists to the underlying smooth muscle. The mechanism of separation of the tight junctions responsible for the hyperpermeability remains speculative, but is believed to involve alterations in the interaction of the

cytoskeleton at the plasma membrane, influencing the integral components of the tight junction, or focal changes in intracellular and/or intercellular levels of $Ca^{2+}$, or both.

Other pulmonary studies have shown that rats exposed to $H_2S$ at 10, 200, or 400 ppm for 4 hr develop necrosis of the nasal epithelium followed by exfoliation of ciliated and olfactory mucosal cells but not of the squamous epithelial cells; these cytotoxic effects, and polymorphonuclear exudation and pulmonary edema, were dose related (76). Resolution proceeded much faster in nasal than in olfactory mucosa, as olfactor cells were still exfoliating 44 hr after exposure. This may relate to clinical reports of olfactory fatigue or paralysis.

The per-acute effects of inhaled $H_2S$ and injected NaHS ($LD_{100}$s) on the lungs of rats were studied (77). At necropsy, all rats in the $H_2S$ group had gross and histological pulmonary edema, characterized by massive extravasation of eosinophilic fluid into the bronchoalveolar space. By contrast, the NaHS group were unaffected. Although the levels of $S^{2-}$ achieved in the brain were identical (28), the effects on the lungs were not. It is not known whether this was due to a concentration difference at the site of action or whether direct access to the alveoli is required.

The DRC for rats exposed to $H_2S$ is very steep, indicating the possible existence of a sensitive physiologic threshold that, once breached, leads to pulmonary edema and, shortly thereafter, to death (78). Others have shown that when rats are pretreated with capsaicin, the C-fibers that innervate the central airways are depleted of substance P, thus removing the airway defense properties mediated by tachykinins (79). When these capsaicin-treated animals were exposed to a concentration of $H_2S$ that causes 20% mortality in controls, they all died. As well, the capsaicin-pretreated animals died faster than controls and showed more pronounced pulmonary edema.

## REPRODUCTION AND DEVELOPMENT

Before 1984, the effects of $H_2S$ on reproductive processes were not well established. The few reports in the literature originated from studies of the effects of "thermal" mineral waters (containing sulfides). These studies claimed that $H_2S$ may be teratogenic and embryotoxic, as well as suppressing the spermatogenic index. The studies lacked scientific merit because they provide few, if any, details of methodology, results, statistical analysis, or adequate controls (6). Adverse effects on reproduction following chronic exposure to $H_2S$ have been described (80); however, the gas was coadministered with $CS_2$, which is well known to be associated with increased toxicity of reproduction (81).

## *Reproduction*

These ambiguous effects and uncertainty of the results warranted further research on $H_2S$-induced effects on reproduction and development. Recent well-controlled studies have provided definitive proof that chronic low-dose (<100 ppm) exposures to $H_2S$ do not produce any significant adverse effects on reproduction in rats (82, 83). At parturition, however, it was observed that some dams exhibited a dose-dependent increase in delivery time (dystocia) that could have resulted in loss of fetuses owing to asphyxiation (82). In vitro studies provided support that this effect may be a result of a reduction or blockade of oxytocin receptors (85).

## *Development*

Pups exposed to $H_2S$ (<75 ppm) in utero and neonatally to day 21 postpartum developed normally, with only a subtle decrease in time of ear detachment and hair growth (82). No significant differences were seen in growth and weight gain, although depression of weight gain occurred in adult rats. Measured glucose levels were significantly elevated in maternal blood, and serum triglycerides were decreased in pups and dams; however, there was no evidence of alterations in alkaline phosphatase, lactate dehydrogenase, or serum glutamate transaminase (83).

The developing or immature organism lacks many defensive mechanisms such as metabolic processes (86). An incomplete blood–brain barrier and the rapid growth characteristics make the brain particularly susceptible to various toxicants (86). Until recently, there was no conclusive evidence that $H_2S$ altered the developing brain. An isolated report (87) suggested that the retarded development and listlessness of breast-fed infants of mothers working in rayon factories was due to $H_2S$. A brief case report (88) described a 20-month-old child with encephalopathies that may have been due to chronic $H_2S$ exposure and that reversed spontaneously.

We have recently documented that chronic exposures to low levels of $H_2S$ (20–75 ppm) can produce subtle but significant alterations in the architecture and growth characteristics of the developing brain in rats (89). Rat fetuses (in utero) and neonatal pups were chronically exposed to low concentrations of $H_2S$ (50–75 ppm, 7 hr per day, 7 days per week) from 5 days postconception to 21 days postpartum. The growth patterns of the dendritic fields of developing cerebellar Purkinje cells were evaluated by using a digitizing method of analysis (89), which quantitates growth of the dendritic trees. Exposure to 20 and 50 ppm of $H_2S$ produced longer branches, an increase in the vertex path length, and variations in the number of branches in particular areas of the dendritic field. The cells also exhibited a nonsymmetrical growth pattern at a time when random terminal branching is normally occurring (89). In another

study, changes in the amino acid content of developing rat brain tissue were determined (90). On postnatal day 21, aspartate, glutamate, and GABA levels in the cerebrum and aspartate and GABA levels in the cerebellum were significantly depressed. At this critical time of development, it is possible that a decrease in neurotransmitter content may reflect a cellular loss or an alteration in the synthesis or release. In preliminary studies we observed that the mean number of cerebellar Purkinje cells was increased by approximately 20% (48), suggesting that the decrease in GABA was unrelated to loss of Purkinje cells. It also appears that the normal perinatal loss of Purkinje cells is suppressed by $H_2S$. Exposure to low concentrations of $H_2S$ also resulted in an initial increase in the level of taurine in the pups, which may have resulted from maternal sources (91). The return to control levels coincided with the approximate time of establishment of the blood–brain barrier (91), but may be a result of development of capacity to metabolize taurine (90). In addition, the dams exhibited inhibition of alkaline phosphatase and cytochrome oxidase in brain (90). These studies provide evidence that chronic exposure to low concentrations of $H_2S$ does affect development of the CNS and may contribute to possible long-term abnormalities in motor function and behavior. It is not yet established whether these effects are reversible in the continued presence of $H_2S$ or following removal; a study longer than 21 days postpartum (i.e. at least 90 days) is required.

## SECONDARY TARGET SYSTEMS

Comparatively little attention has been focused on other organ systems over the past 10 years. Below are summaries of the known effects of $H_2S$ on the various organ systems; the reader is referred to previous reviews (4, 6, 21), or to one of the many regulatory documents, for most bibliography prior to 1982. Recent developments are specifically noted. The broad spectrum of actions and physicochemical properties of $H_2S$ predict that all or at least most organ systems will be affected to some degree.

### *Eye*

In both humans and animals the moist mucous membranes of the eye can be directly exposed to $H_2S$, and at sublethal concentrations the cornea and conjunctiva are usually irritated (keratoconjunctivitis) (6). This was the first reported toxocity of $H_2S$ (1). Common complaints following exposure to $H_2S$ are listed at the beginning of Table 2. If exposure continues, epithelial cells swell and blister and progress to form vacuoles, which may burst into painful but reversible ulcers on the corneal surface. This condition is often referred to as "sore eye" or "gas eye" (93). In severe cases, ulceration of the cornea has led to scar formation and permanent visual impairment. Recently it has been

shown that an increase in epithelial cells collected by an eye wash (conjunctival cells increasing relative to corneal cells) constitutes an objective measure of ocular irritation by $H_2S$ (93).

### *Olfactory System*

One of the most common complaints of individuals exposed to low concentrations of $H_2S$ is the unpleasant odor. The odor threshold of $H_2S$ is very low compared with many other chemicals (21); however, at concentrations over 100 ppm there is an apparent loss of the smell sensation, which is said to be due to olfactory fatigue. However, fatigue or paralysis of the olfactory nerve has seldom been referenced to an original source, and this well-accepted belief should be reexamined (5). Prolonged exposure may result in a lower threshold for olfactory fatigue (3), although this also has been disputed (5). Nevertheless, the odor of $H_2S$ at low doses may not provide an adequate warning. Since sensitivity appears to diminish with age, it is likely that older persons in the workforce will have higher thresholds (21).

### *Skin*

Although the skin is the largest organ of the body and, to various degrees, will come into direct contact with $H_2S$, there have been few reports on the dermal effects of $H_2S$. Some earlier observations at high concentrations have documented discoloration, spots, and rash. Most anecdotal reports describe reversible skin irritation or allergies that are believed to be a result of exposure to low levels of $H_2S$ (<20 ppm), and a few have also documented observations at very high concentrations.

### *Cardiovascular System*

Several clinical reports demonstrate the sensitivity of the human cardiovascular system to $H_2S$. Acute exposure to high concentrations has resulted in transient changes in electrocardiograms as well as decreases in blood pressure. At low concentrations, $H_2S$ may not present any risk to the cardiovascular system (94). Since cardiac muscle is one of the tissues with a high oxygen demand (95), it is likely that some effects of $H_2S$ may not be directly on the myocardium, but secondary to anoxia due to pulmonary edema and CNS effects. Clinical observations have been well substantiated by animal studies. It was demonstrated that acute or chronic exposure of rabbits and guinea pigs to 72 ppm of $H_2S$ or intravenous $Na_2S$ produced ventricular extrasystoles (6). NaHS caused arrhythmias and a progressive increase in tension in isolated rat atria (R. J. Reiffenstein & B. Phipps, unpublished data). Histochemical examination of myocardial tissue from $H_2S$-exposed rabbits also revealed enzymatic changes, suggesting a possible interference with oxidative metabolism and therefore alteration of ionic conductances in the excitable

tissue. In other studies, chronic exposure to lower concentrations of $H_2S$ (10–80 ppm) showed no effect on the heart rate or blood pressure of mice and rats (97). There still exists the possibility that individuals with some form of cardiovascular disease may be more sensitive to the effects of $H_2S$ and thus form a part of society at greater risk of $H_2S$ toxicity (9, 98).

### *Hepatic Tissue*

The few reports describing possible effects of $H_2S$ on liver function are conflicting and inadequate (6). Clinical studies have suggested that the incidence of cholecystitis, cholangitis, and cholelithiasis was higher than normal in oil refinery workers. Data from animal studies are less helpful, describing no effects in mice or rats chronically exposed to $H_2S$ up to 80 ppm (97) or conversely, decreased bile flow in rats treated with 40 mg of $Na_2S$ $kg^{-1}$ (99), enlarged paled livers of mice exposed to 63 ppm for 16 hr, and severe hyperemia of monkey liver exposed to 500 ppm (6).

### *Renal System*

At low concentrations, $H_2S$ appears to have little effect on kidney morphology (97) or enzyme activity; however, earlier studies described changes in the color of mouse kidneys exposed to 63 ppm for 16 hr and pathological changes in exposed rat kidney (6). Histochemical studies of $H_2S$-exposed rabbits revealed some reductions in levels of renal enzymes such as succinic dehydrogenase and alkaline phosphatase, as well as enhancement of acid phosphatase (6). These results, similar to those described for liver function, are inconclusive and require more definitive and controlled studies with both acute and chronic paradigms.

### *Gastrointestinal System*

It is common for individuals exposed to $H_2S$ to experience gastrointestinal symptoms such as nausea, vomiting, diarrhea, and pain. The effects appear to be reversible and non-life-threatening in both humans and other animals (97).

### *Hematopoietic System*

The few documented studies of the effects of $H_2S$ on the hematopoietic system have reported variable results. Both increased and decreased erythrocyte counts were recorded in animals exposed to 1–50 ppm and to very high (>900 ppm) levels of $H_2S$. An increase in a variety of hematological parameters, but a decrease in erythrocyte numbers in mice exposed to $H_2S$ have been reported (100). In contrast, other studies (97) observed no changes in the hematological parameters following chronic exposure to $H_2S$ at 10–80 ppm. A decrease in enzymatic activities associated with heme synthesis occurs in humans exposed to $H_2S$ plus methylmercaptan during wood pulp production

(101, 102). Results of interaction of $H_2S$ with hemoglobin to produce sulfhemoglobin are also contradictory (5, 6).

### *Immune System*

There are a few studies which suggest that $H_2S$ interferes with the immune system. It was concluded in one study involving *Staphylococcus* challenge in rats exposed to 45 ppm of $H_2S$ that secondary infection due to depression of macrophage function may occur following $H_2S$ exposure (62). This was recently confirmed in an epidemiology study (8).

The possibility of allergic or enhanced anaphylactic response has also been implicated in one early study (6), but the response in rabbits was opposite to that in guinea pigs; this creates some doubt about the validity of the results and their interpretation.

### *Endocrine System*

Possible alteration of endocrine functions has also been suggested by a decrease in milk production in cows exposed to 20–50 ppm of $H_2S$ and by a 50% increase in plasma cortisol levels in goats at 100 ppm. Dose-dependent lesions of rat thyroid gland following administration of 14–28 ppm of $H_2S$ have also been reported (6).

### *Psychological Effects*

Behavioral and psychological effects of $H_2S$ (see Table 2) have been discussed in several earlier studies, and there is a recent report of persistent cognitive impairment of three patients following acute exposure to $H_2S$ (103). A recent case of "knockdown" (unconsciousness) resulted in permanent retrograde amnesia (I. M. O. Vicas, personal communication). The offensive odor is often interpreted as dangerous or life-threatening, and this could induce a variety of both psychological and neurophysiological reactions.

### *Carcinogenesis*

There has been very little activity in research concerning the carcinogenic, mutagenic, or teratogenic effects of $H_2S$ in humans and other animals; the reported genotoxic effects may be limited to cytotoxicity (6). Further investigations in validated test systems are obviously required.

## CLINICAL APPLICATIONS

Diagnosis of exposure to $H_2S$ is usually a matter of circumstance. There are a wide variety of symptoms (Table 2), not all of which may be present.

**Table 2** Clinical symptoms after $H_2S$ exposure[a]

| | | |
|---|---|---|
| "Felt ill" | Headache | Depression |
| Visual "fogging" | Insomnia | Irritability |
| Conjunctivitis | Sore throat/cough | Amnesia |
| Photophobia | Chest pain | Disequilibrium |
| Tearing | Dyspnea | Convulsions |
| Eye pain | Hemoptysis | Pulmonary edema |
| Nausea | Lethargy | Cyanosis |
| Vomiting | Abnormal peripheral reflexes | Unconsciousness |
| Anorexia | Weakness of extremities | Bradycardia |

[a] Compiled from several sources (2, 7, 108).

## *Forensic Detection of $H_2S$ Poisoning*

Confirmation of sublethal exposure has been difficult until the recent development of a simple method for detecting blood sulfide levels (105). Even so, the procedure is too long to provide rapid diagnosis. Sulfide levels are still elevated in blood samples taken 2 hr after exposure (101, 102). In addition, some enzyme levels remain depressed long after the exposure (101, 102). After lethal exposures, the brain sulfide content can now be measured for forensic purposes (22, 23). To date this procedure has been used to determine the cause of death in four cases of suspected $H_2S$ poisoning (106); one of these was determined not to directly involve $H_2S$. The use of dithiothreitol in this test should improve the differentiation between normal and poisoned individuals, although this has only been tried in animals thus far (32).

## *Therapeutic Management of $H_2S$ Poisoning*

The initial events in recovery are the most important, and immediate removal to fresh air is paramount (but inadequately equipped rescuers often become victims). Most victims, even though they may be unconscious, appear to recover spontaneously if they are breathing. If they are not, assisted breathing should be instituted immediately, with full cardiopulmonary resuscitation if there is no heartbeat (107). Given the low level of $H_2S$ exhaled, there would appear to be no danger to the rescuer in the use of mouth-to-mouth respiration (107). Only then should other measures be instituted. Two such approaches have been advocated: scavenging sulfide with methemoglobin formed by administration of nitrites, and administration of hyperbaric oxygen.

NITRITES Nitrite does protect against subsequent poisoning in animals (108), but there are few cases in which treatment after exposure can be shown to have affected the outcome. One early survey (109) suggested that nitrites were of little use. Four recent case reports (110–113) give conflicting evi-

dence of the value of nitrites. It has been suggested (5) that nitrites may be of use only if given within minutes after the $H_2S$ exposure.

OXYGEN Although nitrite did protect against sulfide toxicity, the same study showed that 100% $O_2$ at atmospheric pressure had no beneficial effect (108). There are two case reports of the use of hyperbaric $O_2$ therapy (112, 113) (in which nitrites were also used). In the first there was evidence of pulmonary edema, when the hyperbaric $O_2$ undoubtedly increased $O_2$ delivery. In the latter case, after extensive but ineffective treatment with nitrites, 12 treatments with hyperbaric oxygen were given over 6 days before the patient was asymptomatic. This cannot be distinguished from normal recovery. One other patient (I. M. O. Vicas, personal communication) was unconscious for several hours and regained consciousness during hyperbaric oxygen therapy; however, this individual had severe, apparently permanent, retrograde amnesia. Although this therapy is modeled after treatment for cyanide poisoning (113), it is still unclear whether hyperbaric oxygen affects the outcome of $H_2S$ poisoning (107). Even if the increased partial pressure of the oxygen competitively reactivated oxidative cytochromes, as has been suggested (113), it is possible that the action of ATP thus produced is still inhibited by sulfide.

PERSULFIDE REAGENTS Some enzymes remain inhibited far beyond the time to apparent recovery, e.g. some blood enzymes returned to normal only 2 months after the $H_2S$ poisoning (101, 102). This suggests that some of the sulfide remains firmly bound and is not removed by lowering the plasma sulfide levels by scavenging or metabolism. It should be possible to actively remove this $HS^-$ ion by persulfide reagents. Dithiothreitol given 20 min before NaHS provided significant protection in rats (32, 44); however, death was too rapid for this agent to provide resuscitation if given after the NaHS. Dithiothreitol administration increases the amount of sulfide recovered from the brain tissue of poisoned animals and reverses the inhibition of MAO by $HS^-$ (32). It also restores contractile function in oxidant-injured cardiac muscle (114). This might be doubly useful, since the 1975 report of increased cardiovascular mortality among workers exposed to $H_2S$ (98) has recently been confirmed (9), and there are a number of reports of prolonged arrhythmias following exposure of animals to $H_2S$ (6; see also Cardiovascular System). Interventions that actively remove sulfide from the sites causing inhibition of enzymes, or altered control of ion channels, should hasten recovery. Antidotes suitable for use in the field, especially in situations in which almost immediate death occurs, are unlikely to be found (5). However, in cases of extended unconsciousness, when the victims are hospitalized while still alive, this approach should be considered.

## SUMMARY

Significant progress had been made in determining the action of sulfide on the primary target organs. It is reasonably clear that sulfide causes both $K^+$-channel-mediated hyperpolarization of neurons and potentiation of other inhibitory mechanisms. It is not clear whether these processes are similar to those that occur in anoxia. Changes in perinatal and adult brain neurotransmitter content and release may be related to clinical impairment of cognition. $H_2S$ exposures at concentrations below the current occupational limits cause physiological changes in pulmonary function, thus suggesting that asthmatics are at risk. Studies of fetal and neonatal brain tissue have shown an abnormal development, and the long-term consequences of these neuronal changes have not yet been assessed. Finally, new approaches to therapy are required, such as the use of agents that actively remove sulfide from its sites of action. This may prove more useful in preventing some of the long-term adverse sequelae than the use of nitrites and hyperbaric $O_2$, although the latter should be used in cases of pulmonary edema.

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# Acute effects of hydrogen sulfide inhalation in healthy men and women

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Humans face the risk of acute, sub-acute and chronic exposure to hydrogen sulfide as a result of air pollution, occupational exposures and industrial accidents. The toxicity of hydrogen sulfide has not been elucidated in humans. The current evidence indicates that inhalation of 2 to 10 ppm of hydrogen sulfide for 15–30 min does not effect pulmonary function in healthy men and women. Some asthmatics may demonstrate signs of bronchial constriction as a result of exposure to 2 ppm hydrogen sulfide for 30 min. Oral inhalation of 5 and 10 ppm hydrogen sulfide for 30 min from a closed bag system does not have any significant effect on arterial blood gases and cardiovascular responses during exercise at 50% of maximal aerobic power in aerobically fit men and women. However, exposure to 10 ppm hydrogen sulfide significantly reduces oxygen uptake and increases blood lactate under these conditions in both genders. Skeletal muscle tissue analysis indicates no significant alteration in muscle lactate and enzymatic markers of anaerobic and aerobic metabolism. There is a tendency for a shift in the overall metabolic profile of the skeletal muscle towards anaerobic metabolism. However, the results are not statistically significant because of the small sample sizes. Overall, there appears to be a significant relationship between the maximal aerobic power and the accumulation of lactate resulting from hydrogen sulfide exposure. These acute exposures do not elicit symptoms such as headache, nausea, eye and throat irritation commonly associated with hydrogen sulfide exposure, despite the high ventilation rates during exercise. This could be due to the fact that the subjects were unable to smell the gas and the eyes were not exposed to it. The results of these acute studies have been used to establish ambient air quality standards by governmental agencies in the United States. Future research should focus on identifying specific biological markers and applying non-invasive methods (e.g., near-infrared spectroscopy) for evaluating the toxicity of hydrogen sulfide in humans.

**Keywords:** *air quality standards, human toxicity, hydrogen sulfide inhalation.*

## Human exposure to hydrogen sulfide

### *Risk of Human Exposure to Hydrogen Sulfide*

Hydrogen sulfide, a toxic gas at concentrations above 150 ppm, is utilized or released as a by-product in numerous manufacturing processes associated with the oil and gas, paper pulp, leather tanning, food processing, sewage and textile industries (National Research Council, 1979; World Health Organization, 1981; Beauchamp et al., 1984; U.S. Environmental Protection Agency, 1993). Hence, individuals employed in these sectors are chronically exposed to varying concentrations of this pollutant for prolonged durations. The general population living in the vicinity of these industries usually faces the risk of chronic exposure to low levels of hydrogen sulfide due to atmospheric pollution which occurs from the effluent gases (Spitzer et al., 1989; Kilburn and Warshaw, 1995).

Industrial accidents can result in acute and sub-acute exposures of the general population to hydrogen sulfide. Several major mishaps which resulted in a large number of individuals being exposed to this pollutant, singularly or in combination with others, have been documented. These include: (i) a malfunction of the waste gas flare at a sulfur recovery unit in Poza Rica, Mexico, 1950 which resulted in 22 deaths and 320 hospitalizations (McCabe and Clayton, 1952), (ii) biodegradation of industrial wastes in a 14.5-ha lagoon in Terre Haute, Indiana, 1964 which resulted in 41 health-related complaints (U.S. Public Health Service, 1964), (iii) a sour gas well blow out in Lodgepole, Alberta, 1982 which resulted in two deaths and numerous health-related complaints from the population that was exposed to low concentrations of hydrogen sulfide and sulfur dioxide intermittently for 67 days (Milby, 1983), (iv) a paper pulp mill accident in South Karelia, Finland, 1987 which resulted in an uncontrolled release of hydrogen sulfide for 2 days (Haahtela et al., 1992), and (v) a volcanic lake disaster in northwestern Cameroun which resulted in 1746 deaths resulting from exposure to high concentrations of hydrogen sulfide, sulfur dioxide and carbon dioxide (Afane Ze et al., 1996). There are also numerous reports that have documented 'knock downs' (temporary periods of unconsciousness accompanied by apnea) and fatalities resulting from acute exposures to high concentrations of hydrogen sulfide in the oil and gas industry (Kilburn, 1993), sewage treatment plants (Hall and Rumack, 1997), roofing industry (Hoidal et al., 1986), geothermal plants (Kage et al., 1998), etc.

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*Health Effects of Exposure to Hydrogen Sulfide*

The health effects of hydrogen sulfide inhalation in humans have been documented in several comprehensive reviews (National Research Council, 1979; World Health Organization, 1981; Beauchamp et al., 1984; U.S. Environmental Protection Agency, 1993). It is evident from occupational exposure studies (Burnett et al., 1977; Arnold et al., 1985; Glass, 1990) that prolonged exposure to low concentrations of hydrogen sulfide in the work environment can result in symptoms such as fatigue, weakness in the extremities, headache, nausea, sore throat, insomnia, confusion, eye irritation and gastrointestinal disturbances. Many of these symptoms have also been reported by the general population that has been exposed to low levels of hydrogen sulfide for several days (sub-acutely) as a result of the industrial accidents identified earlier. The reader is directed to these comprehensive reviews for more detailed information on this topic. It is important to note that data from these occupational exposure and epidemiological studies do not provide valid information pertaining to the dose–response relationships of this pollutant due to: (i) variability and uncertainty in the concentration and duration of exposure (Burnett et al., 1977; Arnold et al., 1985), and (ii) the possibility of synergistic effects with other atmospheric pollutants (Jaakkola et al., 1990; Kilburn and Warshaw, 1995).

## Brief review of the toxicity of hydrogen sulfide

In humans, exposure to a pollutant can occur via three main routes: inhalation by the lungs, oral ingestion and absorption via the skin (Smith and Olishifski, 1988). The primary mode of human exposure to hydrogen sulfide is via inhalation. Absorption via the skin or tympanic membrane defect is minimal (Ronk and White, 1985). The detoxification mechanism of hydrogen sulfide is not clearly understood. Majority of the research that has examined the toxicity of hydrogen sulfide has been conducted in the animal species. Reviews (National Research Council, 1979; World Health Organization, 1981; Beauchamp et al., 1984; U.S. Environmental Protection Agency, 1993) pertaining to the toxicity of this substance are in general agreement that when a low concentration of the gas is inhaled, it is readily detoxified by oxygen bound to hemoglobin in the blood. During this process, the sulfide is oxidized to a sulfate or a thiosulfate which is excreted by the kidneys. It is postulated that a small of amount of hydrogen sulfide which cannot be detoxified by the blood, undergoes a similar reaction by oxygen that is bound to myoglobin, a protein that is found only in skeletal muscle. The concentration of myoglobin in muscle tissue is small, and therefore, this is not considered to be a major method of detoxification. The remaining trace amount of unoxidized hydrogen sulfide is eliminated by the lungs. Thus, at low concentrations, hydrogen sulfide is not considered to be a cumulative toxin because it is rapidly detoxified in the blood.

At high concentrations, the capacity to detoxify hydrogen sulfide is exceeded, and the pollutant interferes with mitochondrial respiration in various tissues (National Research Council, 1979; World Health Organization, 1981; Beauchamp et al., 1984; U.S. Environmental Protection Agency, 1993). *In vitro* observations using purified enzyme systems and animal exposure studies have documented that high levels of sulfide can inhibit energy metabolism in various tissues. It appears that hydrogen sulfide is oxidized in the mitochondria by a complex series of reactions in the electron transport chain which involve the utilization of oxygen (Petersen, 1977; Nicholls and Kim, 1982; Powell and Somero, 1986). It tends to inhibit the activity of cytochrome oxidase (aa3) (Torrans and Clemens, 1982; Lopez et al., 1987; Khan et al., 1990), the terminal enzyme in the electron transport chain, which results in oxygen utilization and production of chemical energy in the form of adenosine triphosphate. By inhibiting the activity of this enzyme, the pollutant exerts its toxic effects by depriving the cell of energy that is essential to sustain its function. In this regard, the pollutant is considered to be analogous to hydrogen cyanide (Smith and Gosselin, 1979). Other evidence indicates that glycolytic (Torrans and Clemens, 1982) and amino acid metabolism in the brain (Kombian et al., 1988; Hannah et al., 1989; Reiffenstein et al., 1992) are also adversely effected at high concentrations of hydrogen sulfide. The lethal effects of acute hydrogen sulfide intoxication in animals seem to be due to respiratory paralysis resulting from such exposures (Ammann, 1986; Guidotti, 1996) and not from cerebral necrosis (Baldelli et al., 1993). It is also noteworthy that the toxic effects of hydrogen sulfide seem to depend upon the mode of exposure in the animal species. Lopez et al. (1989) demonstrated that in the rat model, intraperitoneally injected sulfide was not able to mimic the pulmonary alterations induced by lethal peracute exposure to an atmosphere containing hydrogen sulfide. It is imperative, therefore, that when studying the toxicity of hydrogen sulfide in humans, the subjects be allowed to inhale the gas, so that the validity of the findings can be maximized.

## Theoretical considerations for studying the toxicity of hydrogen sulfide in humans

*Dependency on the Ventilation Rate*

The overall dose of a pollutant is determined by the concentration of the pollutant, duration of exposure and ventilation rate (Smith and Olishifski, 1988). For a given concentration and duration of hydrogen sulfide exposure in

humans, the dose administered is dependent on the ventilation rate, because the pollutant is absorbed into the body via the pulmonary system (National Research Council, 1979; World Health Organization, 1981; Beauchamp et al., 1984; U.S. Environmental Protection Agency, 1993). In humans, the ventilation rate (expressed in liters per minute, l/min) is determined by the individual's work rate. During the transition from rest to maximal work (as on a cycle ergometer or treadmill), the ventilation rate increases in an exponential manner (Astrand and Rodahl, 1986; Wasserman et al., 1994). Initially, the ventilation rate changes linearly with work rate and oxygen uptake until the lactate threshold (defined as the work rate at which a significant amount of lactate accumulates in the blood) is attained. At higher work rates, lactate accumulates in the blood in an exponential manner due to an imbalance between oxygen supply and demand. This lactate is buffered by bicarbonate in the blood and elevates the arterial carbon dioxide tension, thereby providing an additional stimulus to ventilation via the peripheral chemoreceptors. As a result, the ventilation rate increases exponentially during incremental exercise. The lactate threshold is also referred to as the ventilatory threshold and it usually occurs at 40% to 50% of the maximal aerobic power ($VO_{2max}$) in healthy subjects. The exponential relationship between work rate and ventilation rate implies that when individuals are working in a hydrogen sulfide environment, the overall dose will be substantially greater at the higher work rates. In healthy subjects, typical ventilation rates range from approximately 8 l/min at rest to 125 l/min during maximal exercise.

*Availability of Oxygenated Blood*

It is evident from the biological mode of action of hydrogen sulfide described earlier that the capacity of the body to detoxify it will be directly related to the availability of oxygenated blood. This is dependent upon the blood volume, hemoglobin concentration and cardiac output (Astrand and Rodahl, 1986). The cardiac output is defined as the volume of blood that is ejected by the left ventricle per unit time (usually expressed in l/min). For a given blood volume and hemoglobin concentration, the ability to detoxify hydrogen sulfide will be dependent upon the cardiac output. During the transition from rest to maximal work, the cardiac output increases in a linear manner, until the maximal work rate or $VO_{2max}$ is attained (Astrand and Rodahl, 1986; Wasserman et al., 1994). However, the magnitude of the increase in cardiac output during this transition is considerably lower than that of the ventilation rate. Therefore, when the ventilation–perfusion ratio (i.e., the ratio between alveolar ventilation rate and cardiac output) is calculated, the values increase in an exponential manner. This trend is determined by the ventilation rate. Typical values for the ventilation–perfusion ratio range from 0.8 at rest to approximately 5 or more during maximal work (McArdle et al., 1996).

The fact that the ventilation–perfusion ratio increases exponentially with work rate implies that the capacity to detoxify hydrogen sulfide progressively diminishes because the amount of oxygenated blood per unit volume of air ventilated is significantly lowered. Theoretically, at work rates below the ventilatory threshold, the capacity to detoxify the hydrogen sulfide will be quite high because there is sufficient oxygenated blood available for this purpose. However, when the ventilatory threshold is exceeded, the amount of oxygenated blood available for detoxification decreases at a much faster rate with respect to the ventilation rate, and the pollutant exerts its toxic effects on the various tissues. This theoretical model for the detoxification of hydrogen sulfide is illustrated in Figure 1. It should also be noted that the availability of oxygenated blood is approximately 10% lower in women compared to men because of their lower blood volumes (per kilogram of body weight) and hemoglobin concentrations (Astrand and Rodahl, 1986). This suggests that women may be susceptible to the toxic effects of hydrogen sulfide than men.

*Aerobic Capacity of the Tissues*

Theoretically, the toxic effects of hydrogen sulfide will be minimized in tissues which have a high aerobic capacity. While there are numerous enzymes that are involved in aerobic respiration in the mitochondria, the primary one that is affected by hydrogen sulfide is cytochrome oxidase aa3 (National Research Council, 1979; World Health Organization, 1981; Beauchamp et al., 1984; U.S. Environmental Protection Agency, 1993). In humans, the activity of this enzyme differs considerably amongst the various tissues such as the brain, heart, lungs and skeletal muscles. This suggests that the toxic effects of hydrogen sulfide will differ in these tissues. In skeletal muscles, there are two major types of motor units which are classified on the basis of their oxidative capacity (Astrand and Rodahl, 1986; McArdle et al., 1996). Histochemical analysis has demonstrated that the slow twitch units (Type I) have a higher aerobic capacity than the fast twitch units (Type II), primarily because of their larger mitochondrial density and greater activity of the aerobic enzymes including cytochrome oxidase. In the human body, there are some muscles that are considered to predominantly slow twitch, while others are classified as fast twitch. Furthermore, since these skeletal muscle characteristics are determined genetically (Komi et al.,

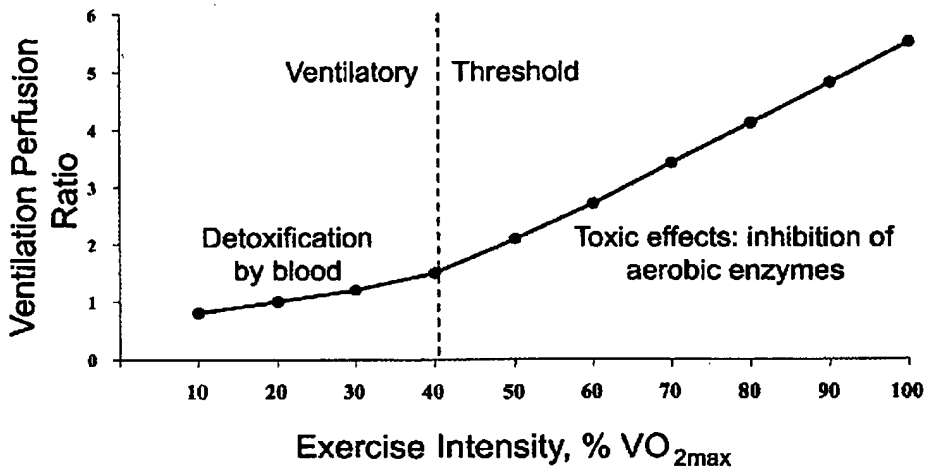


**Figure 1.** Hypothetical model for demonstrating the association between the ventilation–perfusion ratio and the toxicity of hydrogen sulfide at different exercise intensities. The ventilation–perfusion ratio is the ratio between the alveolar ventilation and the cardiac output. This value increases exponentially with exercise intensity, implying that the alveolar ventilation rate increases by a greater proportion than the cardiac output, thereby increasing the toxicity of hydrogen sulfide.

1977), this could be an important factor in the ability of humans to handle hydrogen sulfide.

## Threshold limit values (TLVs) for hydrogen sulfide

TLVs are exposure guidelines that have been established by the American Conference of Governmental Industrial Hygienists (ACGIH, 1993) for airborne concentrations of many chemical compounds. The TLV for a given compound is believed to represent conditions under which nearly all workers may be exposed, day after day, without adverse effects. It is based on the assumption that for any substance, there is some safe and tolerable level which does not induce any adverse effect. The ACGIH has specified three levels of TLVs.

The *TLV-Time Weighted Average (TLV-TWA)* which is defined as the TWA concentration for a normal 8-h work workday and a 40-h work week, to which nearly all workers may be repeatedly exposed, day after day, without any adverse health effect. The *TLV-Short Term Exposure Limit (TLV-STEL)* is the concentration to which workers can be exposed to for a short period of time without suffering from (i) irritation, (ii) chronic or irreversible tissue damage, or (iii) narcosis of sufficient degree to increase the likelihood of accidental injury, impair self-rescue or mutually reduce work efficiency, provided that the TLV-TWA is not exceeded. The TLV-STEL is defined as a 15-min TWA exposure which should not be exceeded at any time during a workday, even if the 8-h TWA is within the TLV-TWA. The TLV-STEL should not occur more than four times a day and there should be at least 60 min between exposures. The *TLV-Ceiling (TLV-C)* is the concentration that should not be exceeded during any part of the working exposure. In the case of hydrogen sulfide, the current TLV-TWA, TLV-STEL and TLV-C are 10, 15 and 20 ppm, respectively. Other US governmental agencies such as the U.S. Department of Labour's Occupational Safety and Health Administration (OSHA, 1993) and the National Institute for Occupational Safety and Health (NIOSH, 1977) have adopted similar standards for human exposure to hydrogen sulfide.

The TLV-TWA for hydrogen sulfide has been set to prevent acute ocular effects such as corneal injury and conjunctivitis (ACGIH, 1993). The validity of this standard is questionable since it is not based on controlled dose-response studies in humans. Instead, it has been established on the basis of observations on humans exposed to hydrogen sulfide in the work environment, where the overall dose (determined by the concentration, duration and ventilation rate) varies considerably. Moreover, the current TLV-TWA for hydrogen sulfide does not consider the effects of the pollutant on physical work performance. Since the overall dose increases exponentially with ventilation rate, it is important to study the acute effects of this pollutant at different work rates so that the validity of the TLV-TWA can be scientifically established.

## Acute effects of low levels of hydrogen sulfide in humans

More than a decade ago, Beauchamp et al. (1984) reported that "the disposition of hydrogen sulfide in humans has not been characterized." Unfortunately, minimal progress has

been made along these lines since then. Much of the information pertaining to the effects of hydrogen sulfide in humans continues to be derived from uncontrolled exposures in the occupational environment (Guidotti, 1996; Guidotti, 1994; Hessel et al., 1997; Milby and Baselt, 1999) and from communities living in the vicinity of this industrial pollutant (Dales et al., 1989; Spitzer et al., 1989; Kilburn, 1997; Kilburn and Warshaw, 1995). While these reports have yielded important findings on the health effects of hydrogen sulfide, this information is limited because: (i) it is difficult to develop dose–response relationships due to the varying concentration, duration and ventilation rate during these exposures, (ii) these studies are not conducive to evaluating the effects of the pollutant on the physiological and biochemical systems in the human body, and (iii) the possibility of other contaminants in the work environment cannot be overlooked (Kilburn, 1997; Kilburn and Warshaw, 1995).

*Review of Controlled Human Hydrogen Sulfide Exposure Studies*

Currently, there are a limited number of controlled studies that have examined the acute effects of low levels of hydrogen sulfide in humans. The results of these studies are summarized in Table 1. The ventilation rates, when available, are provided so as to describe the dose more accurately. Kangas and Savolainen (1987) were the first researchers to report controlled hydrogen sulfide exposures in humans. They exposed healthy volunteers (number and gender not indicated) to 8, 18, and 30 ppm of hydrogen sulfide for 30–45 min in an exposure chamber and collected urine samples periodically for 24 h after the exposure period. The results indicated an increase in urinary thiosulfate which was dependent upon the concentration and duration of exposure. The highest concentration was observed approximately 15 h post-exposure and decreased to the resting values 17 h following the exposure. Recently, Kage et al. (1997) reviewed three cases of hydrogen sulfide poisoning in humans and reported that urinary thiosulfate was the only indicator to prove hydrogen sulfide poisoning in non-fatal cases, while those involving fatalities should include measurement of thiosulfate in the blood. It appears that the results of these human studies support the animal research findings and suggest that the disposition of hydrogen sulfide is similar in both species.

Jappinen et al. (1990) evaluated the acute respiratory effects of hydrogen sulfide inhalation in 26 middle-aged, male pulp mill workers who were chronically exposed to hydrogen sulfide concentrations ranging between 2 and 11 ppm in their work environment. The average hydrogen sulfide concentration was below the TLV-TWA of 10 ppm. Ten asthmatic subjects, three men and seven women, were also evaluated in this study. The subjects inhaled 2 ppm of hydrogen sulfide for 30 min in an exposure chamber. In the pulp mill workers, acute exposure to hydrogen sulfide did not result in any significant change in pulmonary function. The forced vital capacity, forced expiratory volume in 1 s, and bronchial responsiveness to a histamine challenge test were unaffected. Smoking and allergy history, atopy or previous hydrogen sulfide exposure did not seem to have any influence on the results. The asthmatic subjects also did not experience any adverse effect in these respiratory function measurements as a result of the hydrogen sulfide exposure. This group as a whole did not demonstrate any significant change in airway resistance and specific airway conductance. Although two of the subjects demonstrated changes exceeding 30% in these two variables, implying bronchial obstruction, they did not experience any clinical symptom. All the subjects in this study sensed the odour of the gas, but rapidly got accustomed to it. The asthmatics experienced nasal and pharyngeal dryness at the start of the exposure and three of them complained of headaches.

Bhambhani and Singh (1991) and Bhambhani et al. (1994,1996a,b,1997) conducted a series of controlled exercise studies that were designed to test the TLV-TWA for hydrogen sulfide. The investigators used an exercise model because humans who are exposed to hydrogen sulfide in the occupational environment usually perform manual physical work which results in an increase in the ventilation rate and the overall dose of the gas. In the initial dose-response trial (Bhambhani and Singh, 1991), the investigators tested the hypothesis that inhalation of low levels of hydrogen sulfide during exercise would increase dependency upon anaerobic metabolism, possibly due to reduced availability of oxygen and/or inhibition of cytochrome oxidase. Sixteen healthy male volunteers orally inhaled 0 (control), 0.5, 2.0 and 5.0 ppm of hydrogen sulfide from a custom-designed blending and storage system on four separate occasions in random order. The required concentration of the gas was prepared by blending stock hydrogen sulfide and medical air contained in pressurized cylinders at the calculated flow rates. The subjects exercised on a cycle ergometer while inhaling the gas via the mouth. In order to ensure that the subject was "blinded" to the test gas exposure, the nose was blocked off so that he could not smell the gas. The expired air from the subject was continuously monitored by a computerized metabolic cart which measured the following variables: ventilation rate, oxygen consumption, carbon dioxide production and respiratory exchange ratio. Heart rate was recorded using a three-lead electrocardiogram. Blood was withdrawn from the antecubital vein and analysed for its lactate concentration. The cardiovascular and metabolic responses were examined at three exercise intensities: the ventilatory threshold, the threshold of decompensated metabolic acidosis and maximal exercise.

The results indicated that there were no significant changes in the cardiorespiratory and metabolic responses

Table 1. Summary of controlled human hydrogen sulfide exposure studies.

| Researchers | Subjects | Concentration and duration | Exposure mode *Ventilation rate*[a] | Findings |
|---|---|---|---|---|
| Kangas and Savolainen, 1987 | Healthy volunteers, number and gender not indicated | 8, 18, 30 ppm for 30 min | Exposure chamber *Not given* | Increase in urinary thiosulfate proportional to exposure concentration.<br>Peak thiosulfate concentration observed 15 h following exposure. |
| Jappinen et al., 1990 | 26 male pulp mill workers, three male and seven female asthmatics | 2 ppm for 30 min | Exposure chamber *Not given* | No changes in pulmonary function.<br>No significant changes in pulmonary function.<br>Two subjects showed increase in airway resistance and conductance. |
| Bhambhani and Singh, 1991 | 16 healthy men, $VO_{2max}$=41.5±3.6 ml/kg/min | 0, 0.5, 2.0 and 5.0 ppm for an average of 20 min | Oral inhalation from a custom designed system<br>Ventilation at 5 ppm, *VT=44.7 l/min*, *TDMA=81.2 l/min*, *MPO=134.3 l/min* | No changes in cardiovascular and metabolic variables.<br>Significant increase in blood lactate at 5 ppm compared to control exposure.<br>Inverse relationship between $VO_{2max}$ and blood lactate concentration at 5 ppm. |
| Bhambhani et al., 1994 | 13 healthy men, $VO_{2max}$=51.2±7.4 ml/kg/min; 12 healthy women, $VO_{2max}$=40.3±6.4 ml/kg/min | 5 ppm for 30 min | Same as above<br>*Men: 50.3 l/min*, *Women: 43.6 l/min* | No significant changes in arterial blood gases, hemoglobin saturation, cardiovascular and metabolic variables in both genders.<br>No significant change in blood and lactate concentration in both genders. |

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|---|---|---|---|---|
| Bhambhani et al., 1996b | Same as above | Same as above | Same as above | No significant change in muscle lactate concentration in both genders.<br>Significant decrease in citrate synthase activity in men.<br>No significant changes in lactate dehydrogenase and cytochrome oxidase activity in both genders. |
| Bhambhani et al., 1996a | Nine healthy men, $VO_{2max}$=51.5±42.7 ml/kg/min;<br>10 healthy women, $VO_{2max}$=41.5±3.6 ml/kg/min | 10 ppm for 15 min at 50% of $VO_{2max}$ | Same as above<br>*Four to five times resting level* | No significant changes in pulmonary function and diffusing capacity of the lung for carbon monoxide in both genders. |
| Bhambhani et al., 1997 | 15 healthy men, $VO_{2max}$=54.2±8.4 ml/kg/min;<br>13 healthy women, $VO_{2max}$=41.8±4.5 ml/kg/min | 10 ppm for 30 min at 50% of $VO_{2max}$ | Same as above<br>*Men: 50.0 l/min, Women: 36.4 l/min* | Significant decrease in oxygen uptake in both genders.<br>Significant increase in blood lactate in both genders.<br>Inverse relationship between $VO_{2max}$ and muscle lactate concentration.<br>No significant change in lactate dehydrogenase, citrate synthase and cytochrome oxidase activities. |

[a]The ventilation rate measured by the metabolic cart is the expired volumes expressed in liters per minute, BTPS (body temperature and pressure saturated). The inspired volume is approximately 5–10% less than the expired values.

VT=ventilatory threshold, TDMA=threshold of decompensated metabolic acidosis, MPO=maximum power output.

during exercise at the three intensities. The heart rate, ventilation rate, oxygen consumption and carbon dioxide production were unaltered as a result of the hydrogen sulfide exposures. However, inhalation of 5 ppm hydrogen sulfide significantly increased the blood lactate concentration when compared to the control condition by 65%, 56% and 44% at the three exercise intensities, respectively. This observation in humans is consistent with the findings of Torrans and Clemens (1982) who reported large increases in blood lactate concentration in channel catfish exposed to high concentrations of hydrogen sulfide (0.1 mg/l) for 30 min. The current evidence also indicated that the absolute increase in blood lactate was: (i) greater at the higher exercise intensities, and (ii) was inversely related ($r = -0.48$, $p<0.05$) to the $VO_{2max}$ of the subjects, as illustrated in Figure 2. These findings supported the investigators' hypothesis that acute exposure to low levels of hydrogen sulfide increases the dependency on anaerobic metabolism and alters the biochemical profile of exercising muscle. However, it was unclear from these results whether this exaggerated blood lactate response was due to reduced oxygen availability as a result of detoxification of hydrogen sulfide by oxyhemoglobin, or the inhibition of cytochrome oxidase in the exercising tissue.

The fact that the blood lactate concentration at the 5-ppm exposure increased with the exercise intensity and ventilation rate implies that besides the actual concentration and duration of exposure, the ventilation rate is crucial in determining the effects of hydrogen sulfide in humans. Moreover, the association between the increase in blood lactate concentration at maximal exercise and the $VO_{2max}$ of the subjects suggests that the overall aerobic capacity plays an important role in the ability to handle hydrogen sulfide. The $VO_{2max}$ is dependent upon the ability to transport, deliver and utilize oxygen (Astrand and Rodahl, 1986; McArdle et al., 1996). Mathematically, it is calculated by the Fick equation as the product of the maximal cardiac output and the maximal arterio-venous oxygen difference $\{(a-v)O_{2diff}\}$. It is well documented that the $VO_{2max}$ is significantly higher in endurance-trained individuals who stress the cardiorespiratory system (Astrand and Rodahl, 1986; Wasserman et al., 1994). This parameter is also considerably lower in sedentary individuals and those with cardiorespiratory (e.g., heart disease, lung disease), metabolic (e.g., diabetes) and neuromuscular (e.g., muscular dystrophy) disorders (Astrand and Rodahl, 1986; Wasserman et al., 1994). Generally, the changes in $VO_{2max}$ are attributed to concomitant alterations in both cardiac output and $(a-v)O_{2diff}$. The changes in cardiac output are primarily due to reduced blood and cardiac stroke volumes. Some of the factors contributing to the changes in (a-v) $O_{2diff}$ are significant alterations in mitochondrial density of the skeletal muscle and activities of the oxidative enzymes including cytochrome oxidase. It is likely, therefore, that individuals with low $VO_{2max}$ values, healthy or diseased, would be more susceptible to the adverse effects of hydrogen sulfide.

In the next two studies, Bhambhani et al. (1994,1996b) used an exercise model to examine the acute effects of 5 ppm hydrogen sulfide inhalation on the arterial blood gases,

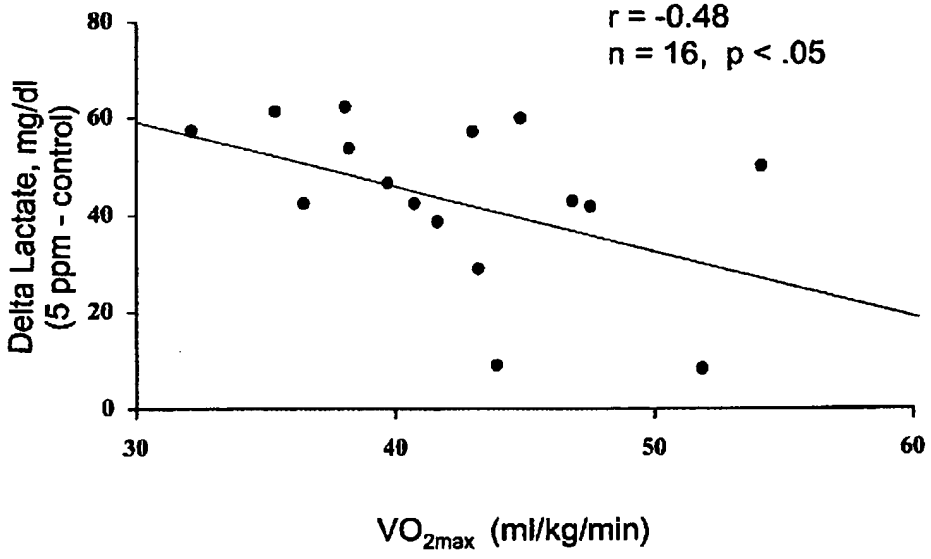


Figure 2. Relationship between the $VO_{2max}$ and change in blood lactate concentration as a result of inhalation of 5 ppm hydrogen sulfide in healthy men. Figure originally appeared in Bhambhani and Singh (1991); reproduced with permission from the American Physiological Society.

cardiovascular and metabolic responses, and biochemical properties of skeletal muscle in healthy men and women. This concentration was used because the earlier study documented a significant increase in blood lactate at this level. The researchers hypothesized that: (i) oral inhalation of hydrogen sulfide would result in significant increases in muscle and blood lactate concentration due to a significant inhibition of aerobic enzyme activities in the skeletal muscle, and (ii) the increases in muscle and blood lactate concentrations would be significantly higher in women compared to men because of their lower hemoglobin concentrations. Thirteen healthy male and 12 healthy female volunteers exercised on a cycle ergometer for 30 min at 50% of their predetermined $VO_{2max}$. This metabolic rate was selected because it was 10% higher than the time weighted average metabolic rate recommended for an eight hour working day to avoid undue fatigue (Shephard,1987). Blood samples were obtained from the radial artery for determination of arterial blood gases and a prewarmed fingertip for measurement of blood lactate prior to and during the final minute of exercise. Arterial hemoglobin saturation was continuously monitored using a pulse oximeter. Cardiorespiratory and metabolic responses were recorded using an automated metabolic cart interfaced with an electrocardiogram. Blood pressure was measured at regular intervals during the test. A muscle biopsy was obtained from the right vastus lateralis muscle under local anaesthesia immediately after the test. The tissue was subsequently analysed for its lactate concentration and activities of the following enzymes: lactate dehydrogenase, a glycolytic enzyme which results in the conversion of pyruvate to lactate and whose activity is increased by exposure to high concentrations of hydrogen sulfide (Torrans and Clemens, 1982; Lopez et al., 1987); citrate synthase, a citric acid cycle enzyme which is routinely used as a marker for aerobic metabolism (Holloszy, 1988); and cytochrome oxidase, the terminal enzyme in the electron transport chain which is known to be inhibited by hydrogen sulfide (Torrans and Clemens, 1982; Lopez et al., 1987; Khan et al., 1990).

In both genders, the 5-ppm exposure did not result in any significant alteration in the: (i) arterial blood gases and hemoglobin saturation levels, (ii) cardiovascular and metabolic responses, and (iii) rate pressure product (product of heart rate and systolic blood pressure), which is considered a valid index of myocardial oxygen consumption (Kitamura et al., 1972). Blood lactate concentrations had a tendency to increase by 10% as a result of the hydrogen sulfide exposure in both genders, but the differences were not statistically significant. The researchers suggested that this was due to the high aerobic fitness level of the male and female subjects. In men, the markers of anaerobic metabolism (muscle lactate and lactate dehydrogenase activity), had a tendency to increase, whereas the two aerobic markers (citrate synthase and cytochrome oxidase) tended to be inhibited by hydrogen sulfide exposure. Statistically, citrate synthase activity was the only enzyme to be significantly affected by hydrogen sulfide. In women, the anaerobic markers were unaffected by hydrogen sulfide exposure, while the activity of cytochrome oxidase demonstrated a tendency to increase. In both genders, negative correlations were observed between the $VO_{2max}$ expressed in ml/kg/min and muscle lactate concentration ($r = -0.47$ in men and $-0.44$ in women). Although these correlations were not statistically significant, most likely due to the small sample size, they do suggest that maximal aerobic power plays an important role in the ability to handle hydrogen sulfide; a finding which supported their earlier observations. While the females did have significantly lower hemoglobin concentrations and activities of the aerobic enzymes than the males, no significant gender differences were observed for any of the biochemical variables as a result of the hydrogen sulfide exposure. The authors attributed this to the lower ventilation rate (20%) or overall dose in females compared to males. The researchers concluded from these two studies that acute exposure to 5 ppm hydrogen sulfide does not: (i) affect autonomic nervous system function because the cardiovascular responses, which are mediated via the medulla oblongata in the brain, did not demonstrate any significant change, and (ii) alter the metabolic profile of exercising muscle in healthy men and women who had high aerobic fitness levels.

In another study conducted by Bhambhani et al. (1997), the investigators examined the acute effects of 10 ppm hydrogen sulfide inhalation on the hematologic, cardiovascular, metabolic and biochemical variables identified above. Twelve males and 11 females completed the same exercise protocol described in the 5-ppm exposure study. The major finding was that oxygen consumption was significantly reduced and blood lactate concentration was significantly elevated in both genders. Since there were no significant changes in arterial hemoglobin saturation and the cardiovascular responses (i.e., total oxygen transport), the investigators hypothesized that the decrease in oxygen consumption and increase in blood lactate could be due to peripheral changes in the exercising muscle. However, muscle lactate and the enzymatic markers of anaerobic and aerobic metabolism identified earlier were unaltered as a result of the exposure. There was a tendency for muscle lactate to increase and citrate synthase activity to decrease as a result of the exposure in both genders. Once again, no significant gender differences were observed for any of the responses. This was most likely due to the lower absolute ventilation rate in females compared to males. Because of the significant reduction in oxygen uptake and the concomitant increase in blood lactate, the investigators questioned the validity of the current 10 ppm TLV-TWA for hydrogen sulfide.

In another report, Bhambhani et al. (1996a) documented the acute effects of 10-ppm hydrogen sulfide inhalation on pulmonary function measures in healthy men and women. Eleven male and nine female subjects who volunteered in the above exercise study also participated in these experiments. The following pulmonary function variables were assessed prior to and following 15 min of cycle exercise at 50% of $VO_{2max}$: forced vital capacity, maximum ventilation volume and diffusion capacity of the lung for carbon monoxide. From the vital capacity maneuver, the following variables were calculated: forced expiratory volume in 1 s, ratio between the forced expiratory capacity in 1 s and the vital capacity, peak expiratory flow rate and forced expiratory flow at 25–75% of the forced vital capacity. The results indicated no significant alterations in any of the variables monitored in either gender. The authors concluded that although inhalation is the primary mode of exposure for hydrogen sulfide in humans, the lung does not seem to be the target organ where the pollutant exerts its toxic effects. These observations were consistent with those of Jappinen et al. (1990) who reported that 30 min of exposure to 2 ppm hydrogen sulfide in an exposure chamber did not have any adverse effect on pulp mill workers and asthmatics.

Several cross-sectional studies have reported on the effects of chronic exposure to hydrogen sulfide on pulmonary function and respiratory symptoms. Hessel et al. (1997) documented that pulmonary function was not adversely affected in oil and gas workers who were exposed to hydrogen sulfide in their occupational environment, even though they were exposed to concentrations strong enough to cause respiratory symptoms. Workers who had experienced a previous "knockdown" also did not demonstrate alterations in pulmonary function, but did report greater shortness of breath while hurrying on the level or walking up a slight hill. A limitation of this study was that the investigators did not measure the degree of dyspnea during walking, but rather, the information was based on recall by the subjects in the study. A report by Richardson (1995) indicated that sewage treatment workers chronically exposed to hydrogen sulfide demonstrated significant reductions in pulmonary function measurements when compared to water treatment workers who were not exposed to the pollutant. Moreover, the decline in pulmonary function was greater in workers presumed to have the highest hydrogen sulfide exposure determined indirectly from their job titles. Community exposure studies (Dales et al., 1989; Spitzer et al., 1989) which have examined the chronic effects of sour gas (which is estimated to have 90% hydrogen sulfide) exposure on pulmonary function have reported no adverse effects in children and adults. However, the children reported a greater incidence of respiratory symptoms when compared to the reference group. The lack of an association between respiratory symptoms and decline in pulmonary function suggested an increased awareness of health in this population or a small biologic environmental effect.

*Implications of the Findings*

It is well documented that elevated muscle and blood lactate concentrations are associated with muscular fatigue in humans (Wenger and Reed, 1976; Roberts and Smith, 1989). Although the exact mechanism has not been elucidated, it is believed that the accumulation of the hydrogen ions associated with increased lactate production decreases intramuscular pH, thereby inhibiting some of the enzymes in the aerobic and anaerobic metabolic pathways. This decreases the rate at which chemical energy can be produced in the muscle cell, which slows down the rate at which physical work can be done, thereby inducing fatigue (Wenger and Reed, 1976). Many of the epidemiological and occupational exposure studies have identified fatigue as a symptom of sub-acute and chronic exposure to hydrogen sulfide (Burnett et al., 1977; Arnold et al., 1985; Glass, 1990). Although the results of some studies published by Bhambhani and Singh (1991) and Bhambhani et al. (1997) documented significant increases in blood lactate, there were no objective or subjective signs of fatigue in these subjects. In the initial study (Bhambhani and Singh, 1991), the maximal power output of the male subjects was unchanged despite a 44% increase in blood lactate as a result of the 5-ppm exposure when compared to the control condition. Similarly, in the subsequent studies (Bhambhani et al., 1994,1997), the subjects did not report any alteration in the rating of perceived exertion during the 30 min of exercise, although there was a tendency for blood and muscle lactate concentrations to increase as a result of this hydrogen sulfide exposure. The rating of perceived exertion is a psycho-physiological variable which has been validated against muscle and blood lactate concentrations during exercise (Borg, 1982; Noble et al., 1989). It subjectively describes the perception of effort during physical work. The researchers felt that the inconsistency of their findings was due to the fact that the subjects were exercising at only 50% of $VO_{2max}$, which resulted in fairly low lactate concentrations (2–4 mmol/l), when compared to those observed during maximal exercise (12–15 mmol/l) (Astrand and Rodahl, 1986). Moreover, in these studies, the subjects exercised for only 30 min at a moderately high ventilation rate; approximately 45 l/min for males and 35 l/min for females. It is unclear how prolonged exposures at higher ventilation rates would influence these results.

*Limitations of the Studies*

A major limitation of the controlled studies performed by Kangas and Savolainen (1987) and Jappinen et al. (1990)

was that the ventilation rate of the subjects was not recorded, thereby making it difficult to quantify the exact dose. It is likely that the subjects were sitting down in the exposure chamber, and under these conditions, the ventilation rate would have been approximately 8–10 l/min. If this was the case, the overall hydrogen sulfide dose would have been quite low and may not be representative of the ventilation rates common during occupational tasks, recreational pursuits and other activities of daily living.

All of the controlled studies conducted by Bhambhani and Singh (1991) and Bhambhani et al. (1994,1996a,b,1997) had several limitations, and therefore, should be interpreted with caution. Firstly, since the subjects were inhaling the gas from a closed bag system, they were unable to smell the gas and the eyes were not directly exposed to the pollutant. Hence, the most likely reason why none of the volunteers in these studies experienced symptoms such as headache, nausea and conjunctivitis that are characteristic of hydrogen sulfide exposure was due to the exposure mode. As discussed earlier, Jappinen et al. (1990) reported that subjects who were exposed to 2 ppm of hydrogen sulfide in an exposure chamber rapidly adjusted to the smell of the gas, but three of them complained of headaches. Winneke (1992) documented that humans exposed to air pollutants with odour and irritant properties such as hydrogen sulfide in an exposure chamber elicit psychophysiological responses in a dose-dependent manner. Hence, future studies should consider using exposure chambers to maximize the validity of the research findings in humans. Secondly, the subjects in all these studies were healthy volunteers who had $VO_{2max}$ values above those expected for their age and gender. The inverse relationship observed between $VO_{2max}$ and the increase in blood and muscle lactate suggests that these subjects were less susceptible to the adverse effects of hydrogen sulfide because of their high maximal aerobic capacity. Since the general population includes healthy, sedentary individuals with lower aerobic capacities, and those with cardiorespiratory, metabolic and neuromuscular disorders, it is likely that this segment of the population would be affected to a greater extent by the hydrogen sulfide exposures. Thirdly, none of the subjects in these studies was previously exposed to hydrogen sulfide on a chronic basis. It has been suggested (National Research Council, 1979; Beauchamp et al., 1984) that such individuals may develop a hypersensitivity to the gas. If this is true, then it is likely that they will demonstrate a greater response to the exposure levels evaluated in these studies. Currently, there is no direct evidence to confirm this hypothesis and specific studies need to be designed for this purpose. Finally, none of these findings have been verified by other research laboratories, and until they can be replicated, they should be interpreted with caution.

## Development of standards for human exposure to hydrogen sulfide

The results of the acute, controlled human exposures to hydrogen sulfide reviewed above have been used to develop air quality standards by the Nebraska Department of Environmental Quality (NDEQ, 1997) and the Agency for Toxic Substances and Disease Registry (ATSDR, 1997). The NDEQ (1997) established a 30-min ambient air quality standard for total reduced sulfur, which is the total amount of sulfur contained in the following compounds: hydrogen sulfide, methyl mercaptan, dimethyl sulfide and dimethyl disulfide. These compounds occur naturally in the environment, with hydrogen sulfide being the largest contributor of the total reduced sulfur content in the atmosphere. Ambient air quality standards are designed to protect the public from adverse health and welfare effects from air pollutants. The ATSDR (1997) develops toxicological profiles for a variety of substances on a regular basis. The minimum risk level (MRL), as described by the ATSDR, is an estimate of the daily human exposure of the substance that is likely to be without appreciable risk of non-cancer health effects. The MRLs are intended to serve as screening levels for potential health effects that may be of concern at hazardous waste sites. They are not intended to define clean-up or action levels.

The NDEQ and ATSDR derived their standards according to inhalation dosimetric methods developed by the U.S. Environmental Protection Agency (1994). The standards were calculated in the manner described below.

$$RfC_i = (NOAEL - HEC)/(UF \times MF)$$

In this equation: $RfC_i$=inhalation reference concentration of the gas, $NOAEL$=no observed adverse effect level, $HEC$=human equivalent concentration, $UF$=uncertainty factor associated with determining a reference concentration from different human or animal databases, $MF$=modifying factor reflecting professional judgement of the entire database of the specific chemical.

The NDEQ developed their ambient air quality standard on the basis of the dose-response study conducted by Bhambhani and Singh (1991). In this study, the researchers reported a significant increase in blood lactate as a result of the 5-ppm exposure, but no change at 2 ppm. Hence, the NOAEL for blood lactate was 2 ppm. Since the study was conducted on humans, an interspecies adjustment factor was not necessary. The value of 10 was used for the UF because the study was conducted on healthy males, and only one uncertainty factor, application to sensitive populations, was applied. A low MF of 2 was built into the standard because the study was well controlled and subjected to peer review. When these values were substituted in the above equation,

the $RfC_i$ calculated was 0.10 ppm for a 30-min exposure. The NDEQ also performed similar calculations using data from the subsequent studies conducted by Bhambhani et al. (1996a) and Jappinen et al. (1990) to confirm the scientific validity of this standard.

The ATSDR derived 0.5 ppm as the 24 h MRL for hydrogen sulfide using the procedure described above. In the development of the MRL, a value of 5 ppm was used as the NOAEL from the study published by Bhambhani et al. (1994). It should be noted, however, that this was not a dose-response study. The results indicated no significant alterations in the cardiovascular and metabolic variables in healthy men and women. As well, no significant changes were observed in the biochemical profile of the exercising muscle (Bhambhani et al., 1996b). Specifically, muscle lactate and the activities of lactate dehydrogenase, citrate synthase and cytochrome oxidase were unchanged in both genders, with the exception of a significant decrease in citrate synthase in the males. A UF of 10 was used to account for variability in human data (presumably from healthy to sensitive populations) and no MF was used in the calculation. Supporting evidence from the studies published by Bhambhani and Singh (1991), Bhambhani et al. (1996a) and Jappinen et al. (1990) was used to corroborate this standard.

## Future research directions for studying human hydrogen sulfide toxicity

In order to increase our understanding of the toxicity of hydrogen sulfide in humans, it is important that well-controlled, dose-response studies be designed to evaluate the physiological, biochemical and health effects of this pollutant. While invasive techniques on the animal species have provided invaluable information pertaining to the toxicity of this substance, the application of such techniques on humans is limited for obvious reasons. Currently, there is an urgent need to identify biological markers that are specific to the toxicity of hydrogen sulfide in humans (Guidotti,1994; Milby and Baselt, 1999). This information will be extremely beneficial in monitoring individuals who may be exposed to hydrogen sulfide in a variety of settings. As well, suitable non-invasive techniques need to be developed for screening purposes.

One particular technique that shows promise for studying the toxicity of hydrogen sulfide on brain and muscle tissue is near-infrared spectroscopy (NIRS). This is a valid non-invasive method of evaluating relative changes in cerebral and muscle oxygenation and blood volume in humans (Mancini et al., 1994; Kleinschmidt et al., 1996). This technique is based on the differential absorption properties of chromophores (light-absorbing compounds) in the near-infrared range; that is, at wavelengths between 700 and 1000 nm of the absorption spectrum. In the brain, the chromophores that can be monitored are hemoglobin and cytochrome oxidase, whereas in skeletal muscle, both these chromophores as well as myoglobin can be monitored. Since these chromophores are the specific action sites for hydrogen sulfide, it appears that this would be a suitable non-invasive technique for studying its toxicity in both the muscle and brain. A recent study (Maehara et al., 1997) demonstrated that this technique is sensitive in detecting changes in oxygenation of muscle tissue in humans exposed to carbon monoxide, a toxic pollutant that binds to hemoglobin in the blood. Another report (Gopinath et al., 1995) indicated that NIRS was useful in predicting the occurrence of subsequent hematomas in brain-injured patients. To date, there are no controlled studies pertaining to the effects of hydrogen sulfide exposure on the human brain. Since neurological and psychological sequelae are frequently reported as a result of hydrogen sulfide exposure (Tvedt et al., 1991; Kilburn, 1993; Snyder et al., 1995), it would be interesting to apply this technique to evaluate whether brain function is altered in these individuals.

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**Environmental Health Criteria 19**

# HYDROGEN SULFIDE



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## NOTE TO READERS OF THE CRITERIA DOCUMENTS

While every effort has been made to present information in the criteria documents as accurately as possible without unduly delaying their publication, mistakes might have occurred and are likely to occur in the future. In the interest of all users of the environmental health criteria documents, readers are kindly requested to communicate any errors found to the Division of Environmental Health, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda which will appear in subsequent volumes.

In addition, experts in any particular field dealt with in the criteria documents are kindly requested to make available to the WHO Secretariat any important published information that may have inadvertently been omitted and which may change the evaluation of health risks from exposure to the environmental agent under examination, so that the information may be considered in the event of updating and re-evaluation of the conclusions contained in the criteria documents.

## ENVIRONMENTAL HEALTH CRITERIA FOR HYDROGEN SULFIDE

A WHO Task Group on Environmental Health Criteria for Hydrogen Sulfide met in Geneva from 24 to 28 March 1980. Mr G. Ozolins, Associate Manager, Environmental Health Criteria and Standards, opened the meeting on behalf of the Director-General. The Task Group reviewed and revised the second draft of the criteria document and made an evaluation of the health risks from exposure to hydrogen sulfide.

The first and second drafts were prepared jointly by Dr T. H. Milby of the Environmental Health Associates, Inc., Berkeley, CA, USA, and Dr R. C Spear of the Department of Biomedical and Environmental Health Sciences, University of California, Berkeley, CA, USA. The comments on which the second draft was based were received from the national focal points for the WHO Environmental Health Criteria Programme in Australia, Belgium, Czechoslovakia, Finland, Federal Republic of Germany, Mexico, New Zealand, Poland, USA and USSR, and from the International Labour Organisation, Geneva, the International Centre for Industry and Environment, France, and the International Petroleum Industry Environmental Conservation Association, London. Comments were also received from Professor M. Katz (Canada) and Professor R. Lilis (USA). Some comments were received after the second draft had been prepared and were reviewed by the Task Group during its meeting. These comments were from the national focal points for the WHO Environmental Health Criteria Programme in Japan and the United Kingdom and from the Commission of the European Communities, Luxembourg, and the International Union of Pure and Applied Chemistry, London.

The collaboration of these national institutions, international organizations and individual experts is gratefully acknowledged. Without their assistance this document could not have been completed.

This document is based primarily on original publications listed in the reference section. However, several recent publications broadly reviewing health aspects of hydrogen sulfide have also been used, including those of the National Research Council, USA (1979) and NIOSH (1977).

Details of the WHO Environmental Health Criteria Programme, including some of the terms frequently used in the documents, can be found in the introduction to the publication "Environmental Health Criteria 1 — Mercury", published by the World Health Organization, Geneva, 1976, now also available as a reprint.

The following conversion factors have been used in this document: hydrogen sulfide: 1 ppm = 1.5 mg/m³, 1 mg/m³ = 0.7 ppm.

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Financial support for the publication of this criteria document was kindly provided by the Department of Health and Human Services through a contract from the National Institute of Environmental Health Sciences, Research Triangle Park, North Carolina, USA — a WHO Collaborating Centre for Environmental Health Sciences.



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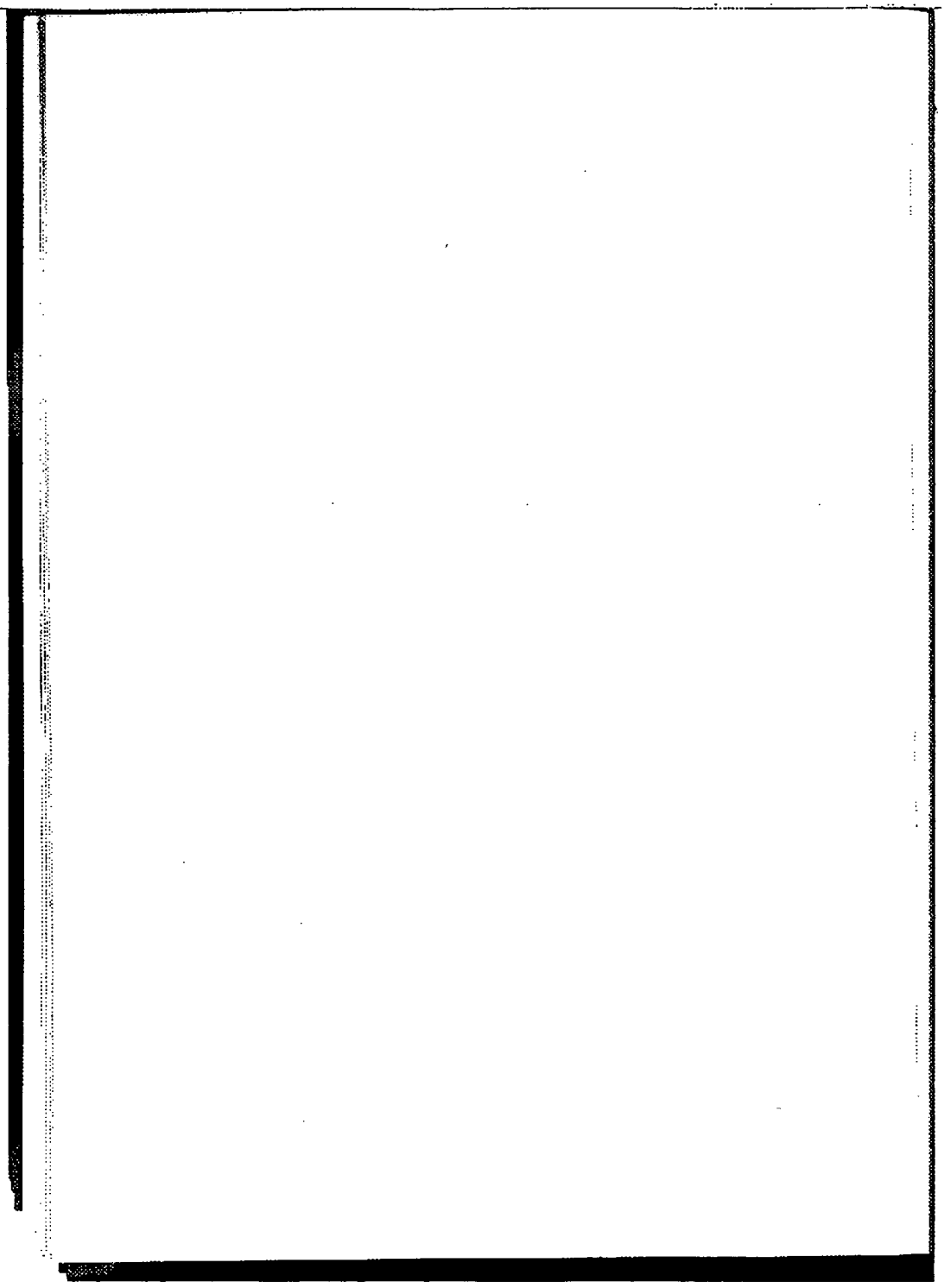

# 1. SUMMARY AND RECOMMENDATIONS FOR FURTHER STUDIES

## 1.1 Summary

### 1.1.1 Properties and analytical methods

Hydrogen sulfide is a colourless gas with a characteristic odour that is soluble in various liquids including water, alcohol, ether, and solutions of amines, alkali carbonates, and bicarbonates. It can undergo a number of oxidation reactions to yield principal products consisting of sulfur dioxide, sulfuric acid, or elemental sulfur. Reaction rates and oxidation products depend on the nature of the oxidizing agent.

The methylene blue colorimetric method has acceptable specificity, accuracy, and sensitivity for hydrogen sulfide determinations, and is generally recognized as a standard analytical procedure. It has been used successfully, in automatic continuous monitoring, but sophisticated maintenance facilities and highly trained technicians are required for this method. Gas chromatography coupled with flame photometric detection is an alternative method for hydrogen sulfide determination, either as a laboratory method or for continuous monitoring in stationary field settings.

Most of the direct-reading methods of hydrogen sulfide determination in the occupational environment are susceptible to various forms of interference. However, methods employing chemical detector tubes appear to be useful in occupational settings, where hazardous levels of hydrogen sulfide can occur. Under these conditions, reliability and accuracy compensate for a certain lack of specificity.

### 1.1.2 Sources of hydrogen sulfide

Hydrogen sulfide is one of the principal compounds involved in the natural cycle of sulfur in the environment. It occurs in volcanic gases and is produced by bacterial action during the decay of both plant and animal protein. It can also be produced by bacteria through the direct reduction of sulfate. Significant concentrations of hydrogen sulfide occur in some natural gas fields and in geothermally active areas.

Hydrogen sulfide can be formed whenever elemental sulfur or certain sulfur-containing compounds come into contact with organic materials at high temperatures. In industry, it is usually produced as an undesirable by-product, though it is an important reagent or intermediate in some processes. Hydrogen sulfide occurs as a by-

product in: the production of coke from sulfur-containing coal, the refining of sulfur-containing crude oils, the production of carbon disulfide, the manufacture of viscose rayon, and in the Kraft process for producing wood pulp.

### 1.1.3 Environmental levels and exposures

Though concentrations of hydrogen sulfide in urban areas may occasionally be as high as 0.050 mg/m³ (0.033 ppm) with averaging times of 30 min—1 h, they are generally below 0.0015 mg/m³ (0.001 ppm). Peak concentrations as high as 0.20 mg/m³ (0.13 ppm) have been reported in the neighbourhood of point sources. In a geothermal area, 1-h mean concentrations of up to 2 mg/m³ (1.4 ppm) have been observed. When hydrogen sulfide was accidentally released in an incident in Poza Rica, Mexico, in 1950, the number of deaths that followed indicated that exposure levels probably exceeded 1500—3000 mg/m³ (1000—2000 ppm).

It is believed that workers are not usually exposed to hydrogen sulfide concentrations above the occupational exposure limits of 10—15 mg/m³ (7—10 ppm) (8-h time-weighted average) adopted by many governments. There are, however, numerous reports of accidental exposures to concentrations that have ranged from 150 mg/m³ (100 ppm) to as high as 18 000 mg/m³ (12 000 ppm). Such massive exposures to hydrogen sulfide have resulted either from leaks in industrial gas streams containing high levels of hydrogen sulfide or from the slow, insidious accumulation of hydrogen sulfide in low-lying areas. The second case may arise when hydrogen sulfide of biogenic origin is generated from such sources as sewage disposal plants and cesspools.

### 1.1.4 Effects on experimental animals

In experimental animals, the effects of high doses of hydrogen sulfide and high doses of cyanide are very similar. Cyanide inhibits the enzyme cytochrome c oxidase [EC 1.9.3.1] [a], thereby interfering with tissue use of oxygen to the point where metabolic demands cannot be met. Hydrogen sulfide also exhibited an inhibitory action on a purified preparation of cytochrome c oxidase.

Results of studies on a number of animal species including canary, rat, guineapig, cat, dog, and goat showed that inhalation of hydrogen sulfide at a concentration of 150—225 mg/m³ (100—150 ppm)

[a] The numbers within brackets following the names of enzymes are those assigned by the Enzyme Commission of the Joint IUPAC-IUB Commission on Biochemical Nomenclature.

resulted in signs of local irritation of eyes and throat after many hours of exposure; at 300—450 mg/m³ (200—300 ppm), eye and mucous membrane irritation appeared after 1 h inhalation and slight general effects after prolonged inhalation; at 750—1050 mg/m³ (500—700 ppm), local irritation and slight systemic signs appeared within 1 h and death after several hours; at 1350 mg/m³ (900 ppm), serious systemic effects appeared in less than 30 min and death within 1 h; at 2250 mg/m³ (1500 ppm), collapse and death occurred within 15—30 min; and, at 2700 mg/m³ (1800 ppm), there was immediate collapse with respiratory paralysis, and death. There is little information on the effects on experimental animals of long-term, low-level exposure to hydrogen sulfide gas.

### 1.1.5 Effects on man

#### 1.1.5.1 *General toxicological considerations*

Hydrogen sulfide is both an irritant and an asphyxiant gas. Its direct irritant action on the moist tissues of the eye produces keratoconjunctivitis, known as "gas eye". When inhaled, hydrogen sulfide exerts an irritant action throughout the entire respiratory tract, although the deeper structures suffer the greatest damage. A consequence may be pulmonary oedema. At concentrations of 1500—3000 mg/m³ (1000—2000 ppm), hydrogen sulfide gas is rapidly absorbed through the lung into the blood, which initially induces hyperpnoea (rapid breathing). This is followed by respiratory inactivity (apnoea). At higher concentrations, hydrogen sulfide exerts an immediate paralysing effect on the respiratory centres. Death due to asphyxia is the certain outcome, unless spontaneous respiration is re-established or artificial respiration is promptly provided. This sequence of events represents the most important toxic effect of hydrogen sulfide.

Acute hydrogen sulfide intoxication can be defined as the effects from a single exposure to massive concentrations of hydrogen sulfide that rapidly produce signs of respiratory distress. Concentrations exceeding about 1500 mg/m³ (1000 ppm) produce such acute effects. Subacute hydrogen sulfide intoxication is the term applied to the effects of continuous exposure for up to several hours to concentrations ranging from 150 to 1500 mg/m³ (100—1000 ppm). In this range of exposure, eye irritation is the most commonly observed effect. However, some reports have indicated that the threshold for eye irritation occurs after several hours of exposure to hydrogen sulfide at levels of 16—32 mg/m³ (10.5—21.0 ppm). Pulmonary oedema may be a more important and potentially fatal complication of subacute hydrogen sulfide intoxication. Chronic intoxication is a largely subjective state characterized by fatigue and believed by some to be a

consequence of intermittent exposure to hydrogen sulfide concentrations of 75–150 mg/m³ (50–100 ppm). Not all research workers accept the existence of such a condition.

The characteristic "rotten egg" odour of hydrogen sulfide is well known. The threshold of perception of this odour varies considerably depending on individual sensitivity, but, under laboratory conditions, it ranges from 0.0008 to 0.20 mg/m³ (0.0005–0.13 ppm). Above about 225 mg/m³ (150 ppm), the gas exerts a paralysing effect on the olfactory apparatus, thus neutralizing the value of its odour as a warning signal. At these concentrations, the odour of the gas has been reported to be sickeningly sweet.

### 1.1.5.2 *Occupational exposure*

Exposure to hydrogen sulfide in high concentrations occurs in numerous occupations. Workers in the oil, gas, and petrochemical industries are occasionally exposed to hydrogen sulfide in concentrations sufficient to cause acute intoxication. In one survey of the petrochemical industry, among 221 cases of hydrogen sulfide poisoning, the overall mortality was 6% and a high proportion of victims exhibited neurological signs and symptoms. Forty percent of all cases required some form of respiratory assistance; 15% developed pulmonary oedema.

Persistent sequelae following acute intoxication have been reported among workers in a number of occupations including sewer workers, chemical plant employees, farmers, shale-oil workers, and laboratory attendants. Most victims who develop sequelae experience a state of unconsciousness during the acute phase of their illness. However, sequelae following acute intoxication without unconsciousness have also been reported.

### 1.1.5.3 *Exposure of the general population*

Several episodes of general population exposure to hydrogen sulfide have been reported. The effects of such exposure have ranged from minor nuisance to serious illness and death. In a small community adjacent to an oilfield installation, large quantities of hydrogen sulfide were released into the air when an oilfield flare malfunctioned. Three hundred and twenty persons were hospitalized, 22 of whom died. Nine exhibited manifestations of pulmonary oedema. Four victims developed neurological sequelae. The air levels of hydrogen sulfide were not measured.

A community of 40 000 people, located in the vicinity of a large geothermal field, was exposed in some areas to hydrogen sulfide levels in air (measured on a continuous basis over a 5-month period)

exceeding 0.08 mg/m³ (0.05 ppm), for, on average, 35% of the time. Although fatal cases of hydrogen sulfide intoxication associated with improper ventilation in geothermal steam-heated dwellings in this area were occasionally reported until 1962, the major problem has been the nuisance caused by the odour of the gas. In a moderately sized community, hydrogen sulfide was released from a small industrial waste lagoon resulting in a 1-h average concentration of hydrogen sulfide in air of 0.45 mg/m³ (0.3 ppm). Complaints were mostly related to the odour of hydrogen sulfide gas. However, the severity of complaints of nausea, vomiting, headache, loss of appetite, and disturbed sleep exceeded the mere nuisance level.

No community studies of the long-term, low-level effects of hydrogen sulfide exposure have been reported.

### 1.1.6 Evaluation of health risks

Hydrogen sulfide in ambient air in concentrations of the order of the odour threshold has not been shown to have any significant biological activity in man or animals. In controlled laboratory studies, the odour threshold for hydrogen sulfide has been reported to range from 0.0008 to 0.20 mg/m³ (0.0005—0.13 ppm). Little information is available on the odour detection limits for hydrogen sulfide either under experimental field conditions or in the ambient air. However, the Task Group considered that a level of 0.008 mg/m³ (0.005 ppm) averaged over 30 min should not produce odour nuisance in most situations. In the occupational setting, the earliest toxic response appears to be eye irritation, which has been reported to occur at 16—32 mg/m³ (10.5—21.0 ppm) after several hours' exposure. The occupational exposure guidelines for hydrogen sulfide recommended by the Task Group included the adoption of a level of 10 mg/m³ (7 ppm) as a workshift time-weighted average value together with a short-term exposure limit of 15 mg/m³ (10 ppm), the latter to be determined as a 10-min or less, average value.

## 1.2 Recommendations for Further Studies

Measurements of hydrogen sulfide concentrations in the ambient air should be included in studies of the levels in air of other common gaseous contaminants, such as the oxides of sulfur and nitrogen. Studies in areas remote from man-made emission sources would provide background data for the development of models for long-distance transport and diffusion, for the evaluation of biological decay processes from natural sources, and for developing a clearer

understanding of global sulfur cycles. More studies are required to elucidate processes involving chemical and photochemical oxidation reactions of hydrogen sulfide. Studies are also necessary to develop methods for the personal dosimetry measurement of hydrogen sulfide that do not require wet chemical techniques.

Studies should be conducted in experimental animals on the cumulative neural effects of repeated and/or continuous long-term hydrogen sulfide exposure at concentrations that induce subacute or chronic intoxication. The cardiac sequelae after acute intoxication should be investigated in intact animals and in those with pre-induced cardiac damage. Studies of the toxicokinetics of absorbed hydrogen sulfide are needed and other studies should be initiated to test for the metabolic generation of hydrogen sulfide from sulfur-containing organic compounds.

Case studies should be made of patients who have suffered acute hydrogen sulfide intoxication to examine the long-term effects on the myocardium. Efforts should be made to estimate the dose of hydrogen sulfide associated with acute poisoning. Prospective studies of new workers to investigate the effects of long-term exposure to concentrations of hydrogen sulfide likely to be encountered in the work place would be valuable. These studies should include considerations of morbidity and mortality, the incidence of cancer and teratogenic effects, and studies of changes in pulmonary function with time. Continuing environmental studies should play a major part in these prospective studies, in order to provide dose-response data, where possible. Similar studies should be initiated among the general population in a geothermal area, taking advantage of the natural conditions provided, for example, by the situation in Rotorua, New Zealand.

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## 2. PROPERTIES AND ANALYTICAL METHODS

### 2.1 Chemical and Physical Properties

Hydrogen sulfide is a flammable colourless gas with the characteristic odour of rotten eggs. It burns in air with a pale blue flame and, when mixed with air, its explosive limits are 4.3% to 46% by volume. Its autoignition temperature is 260°C. The relative molecular mass of hydrogen sulfide is 34.08. Its density is 1.5392 g/litre at 0°C and 760 mm. The ratio density of hydrogen sulfide compared with air is 1.19. One gram of hydrogen sulfide dissolves in 187 ml of water at 10°C, in 242 ml of water at 20°C, in 314 ml of water at 30°C, and in 405 ml of water at 40°C (calculated from Weast, 1977–78). It is also soluble in alcohol, ether, glycerol, and in solutions of amines, alkali carbonates, bicarbonates and hydrosulfides. The vapour pressure of hydrogen sulfide is $18.75 \times 10^5$ Pa at 20°C and $23.9 \times 10^5$ Pa at 30°C. Its melting point is −85.5°C and its boiling point is −60.3°C (Macaluso, 1969; Windholz, 1976).

Hydrogen sulfide can undergo a large number of oxidation reactions, the type and rate of the reaction and the oxidation products depending on the nature and concentration of the oxidizing agent. The principal products of such reactions are sulfur dioxide, sulfuric acid, or elemental sulfur. Aqueous solutions of chlorine, bromine, and iodine may react with hydrogen sulfide to form elemental sulfur. In the presence of oxides of nitrogen, the oxidation of hydrogen sulfide in the gas phase may result in the formation of sulfur dioxide or sulfuric acid but, in aqueous solution (pH 5–9), the primary product is elemental sulfur (Macaluso, 1969).

Hydrogen sulfide dissociates in aqueous solution to form 2 dissociation states involving the hydrosulfide anion ($HS^-$) and the sulfide anion ($S^=$). The pKa in 0.01–0.1 mol/litre solutions at 18°C is 7.04 for $HS^-$ and 11.96 for $S^=$. At the physiological pH of 7.4, about one-third of the total sulfide remains as the undissociated acid and about two-thirds as the $HS^-$ ion. The undissociated hydrogen sulfide in solution is in dynamic equilibrium at the air-water interface with gaseous hydrogen sulfide (National Research Council, USA, 1977).

### 2.2 Atmospheric Chemistry

The atmospheric chemistry of hydrogen sulfide and other sulfur compounds involves chemical and photochemical oxidation reactions of emissions from both natural and man-made sources. The eventual oxidation products are sulfuric acid ($H_2SO_4$) and/or sulfate ion ($SO_4^=$).

There have been relatively few studies of the persistence and conversion of hydrogen sulfide under atmospheric conditions. Krasovitskaja and her co-workers (Krasovitskaja et al., 1965) studied the relationship between concentrations of hydrogen sulfide, sulfur dioxide, carbon monoxide, and hydrocarbons, and the distance from their industrial sources. Hydrogen sulfide concentrations dropped by a factor of 2 between the immediate neighbourhood of the source and a 2.5 km radius. A further decrease in concentration ranging from 30% up to a factor of 8 occurred between the 2.5 km and 20 km radii. These decreases were, in general, greater than those observed for any of the other pollutants measured. Andersson et al. (1974) reported studies concerning the photolysis of hydrogen sulfide and its reaction with sulfur dioxide, as well as its reactions with atomic and molecular oxygen and with ozone.

Junge (1963) calculated that the residence time of hydrogen sulfide was approximately 1.7 days in the presence of an ozone level of 0.05 mg/m$^3$. A similar residence time was estimated by Katz (1977) using data from the global budget of the sulfur cycle presented by Kellogg et al. (1972). Robinson & Robbins (1970) found a residence time in relatively clean air of about 2 days, compared with only about 2 h in a polluted urban atmosphere.

Considerably lower values than those of the previously mentioned investigators, based on the global sulfur budget, have been presented by Granat et al. (1976), on the basis of a very much lower release of sulfur compounds from the biological dacay of organic matter from land and sea. Clearly, this represents a subject that requires further studies involving the measurement of atmospheric concentrations in relatively clean areas on land and elsewhere.

### 2.3 Sampling and Analytical Methods

Because levels of hydrogen sulfide in air, which are of interest as far as human health in concerned, range from highly concentrated industrial gas streams to ambient air pollution levels, numerous analytical methods have been applied. A recent review of current methods can be found in Becker (1979). A further complication in determining air levels of hydrogen sulfide is that according to the air monitoring application, sampling may be on either an intermittent or a continuous basis. Intermittent samples have been taken in plastic bags, evacuated bottles, Tutweiler burets (Shaw, 1940), and detector tubes (West, 1970). Continuous samples have been taken by exposing chemically treated paper tapes (Sanderson et al., 1966; Peregud et al., 1971) or ceramic tiles (Gilardi & Manganelli, 1963) to air, by pumping air through a lead acetate solution, by bubbling air through impingers containing absorbing or colori-

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metric solutions (Goldman et al., 1940), and by using long-duration detector tubes or electronic detectors (West, 1970; ACGIH, 1972; Thompkins & Becker, 1976). Qualitative hydrogen sulfide detection has been based on the blackening of coins, keys, lead-based paint, and lead-acetate treated papers. More recently, direct reading instruments have been developed that make real-time monitoring possible. In some of these instruments, a 2-step absorption-reaction procedure is involved whereas in others, the gas reacts directly with, for example, metal-oxide-coated chips, the electrical properties of which change in response to various gas concentrations. Gas chromatographic methods of analysis have been developed and are particularly used by oil and gas production companies (Stevens et al., 1971). A recent report of the US National Institute for Occupational Safety and Health (NIOSH, 1977) summarizes the current situation with special reference to automatic and/or portable samplers. The report concludes that wet chemical methods are attractive because of their specificity and precision, but that they are less desirable on the basis of the portability and maintenance characteristics of the equipment. Direct reading solid state devices, on the other hand, are portable and relatively rugged but are often nonspecific and susceptible to cross-sensitivities.

However, the practical importance of such cross-sensitivities depends a great deal on the type of study. In ambient air pollution studies in which hydrogen sulfide can be excepted to be in the 0.0015—0.075 mg/m³ (0.001—0.050 ppm) concentration range, interference may be of much greater practical concern than in industrial settings in which concentrations may reach from 30 to 75 mg/m³ (20 to 50 ppm) or more, on occasion, and in which the presence and identity of interfering compounds are often known.

Because of the diversity of circumstances under which hydrogen sulfide has to be determined, only the two principal methods of analysis for hydrogen sulfide are described in detail in the following section. Questions of sampling and analysis suitable for several specific practical applications are also discussed.

### 2.3.1 The methylene blue method

The methylene blue colorimetric method has been evaluated and recommended by various research workers (Jacobs, 1965; Bamesberger & Adams, 1969) and by some institutions such as the US National Institute for Occupational Safety and Health (NIOSH, 1977). This method has also been proposed by the International Organization for Standardization (ISO, 1978). The Intersociety Committee of the American Public Health Association has published detailed procedures of this method for assessing hydrogen sulfide both in the ambient air and in workplace air (Intersociety Committee, 1977a).

Although light, mercaptans, sulfides, nitrogen dioxide, and sulfur dioxide can cause interference, and instruments incorporating both the absorption and reaction functions are not portable, the methylene blue method appears to combine adequate specificity with good accuracy and precision and extreme sensitivity. It can be used with either manual or automatic sample collectors and, in the latter case, with continuous sampling, levels of hydrogen sulfide as low as 0.003 g/m³ (0.002 ppm) can be detected (Levaggi et al., 1972).

In the Intersociety Committee method, hydrogen sulfide is collected by aspirating a measured volume of air through an alkaline suspension of cadmium hydroxide. The sulfide is precipitated as cadmium sulfide to prevent air oxidation of the sulfide, which occurs rapidly in an aqueous alkaline solution. Arabinogalactan is added to the cadmium hydroxide slurry to minimize the photodecomposition of the precipitated cadmium sulfide. The collected sulfide is subsequently determined by spectrophotometric measurement of the methylene blue produced by the reaction of the sulfide with a strongly acid solution of *N*, *N*-dimethyl-*p*-phenylenediamine and ferric chloride. The analysis should be completed within 24—26 h of collection of the sample.

This method is intended for the determination of hydrogen sulfide concentrations in the range of 0.0012—0.1 mg/m³ (0.0008—0.07 ppm). For concentrations above 0.08 mg/m³ (0.05 ppm), the sampling period can be reduced or the volume of liquid increased either before or after aspirating. Excellent results have been obtained using this method for air samples containing hydrogen sulfide concentrations in the range of 7.5—75 mg/m³ (5—50 ppm). This method is also useful for the measurement of source emissions. For example, 100 ml cadmium sulfide-arabinogalactan medium in Greenberg-Smith impingers and 5-min sampling periods have been used successfully.

The methylene blue reaction is highly specific for sulfide at the low concentrations usually encountered in ambient air. Strong reducing agents (e.g., sulfur dioxide) inhibit colour development. Even solutions containing several micrograms of sulfide per millilitre show this effect and must be diluted to eliminate colour inhibition. If sulfur dioxide is absorbed to give a sulfite concentration in excess of 10 μg/ml, colour formation is retarded. Up to 40 μg/ml of this interference, however, can be overcome by adding 2—6 drops (0.5 ml/drop) of ferric chloride instead of a single drop for colour development, and extending the reaction time to 50 min. On the other hand, nitrogen dioxide gives a pale yellow colour with the sulfide reagents at concentrations of 0.5 μg/ml or more. No interference is encountered when 0.57 mg/m³ (0.3 ppm) of nitrogen dioxide is aspirated through a midget impinger containing a slurry of cadmium hydroxide-cadmium sulfide-arabinogalactan. If hydrogen sulfide and nitrogen dioxide are simultaneously aspirated through cadmium hydroxide-arabinogalactan, slurry, lower results

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are obtained, probably because of the gas-phase oxidation of the hydrogen sulfide prior to precipitation as cadmium sulfide.

Using permeation tubes as a source of hydrogen sulfide, a relative standard deviation of 3.5% and a recovery of 80% have been established. The overall sampling and analytical precision is 12.1% relative standard deviation.

Hydrogen sulfide is readily volatilized from an aqueous solution, when the pH is below 7.0. Alkaline aqueous sulfide solutions are very unstable because the sulfide ion is rapidly oxidized by exposure to the air.

Cadmium sulfide is not appreciably oxidized, even when aspirated with pure oxygen in the dark. However, exposure of an impinger containing cadmium sulfide to laboratory or more intense light sources produces immediate and variable photodecomposition. Losses of 50%—90% of sulfide have been routinely reported by a number of laboratories. Even though the addition of arabinogalactan to the absorbing solution controls the photodecomposition, it is necessary to protect the impinger from light at all times. This is achieved by the use of low actinic glass impingers, paint on the exterior of the impingers, or aluminium foil wrapping.

The Intersociety Committee (1977a) has described the apparatus, reagents, and calibration methods suitable for use with midget impinger samplers and appropriate for determining air concentrations of 0.0012—0.1 mg/m³ (0.0008—0.07 ppm). In this range, calibration is recommended using PTFE permeation tubes. In the higher concentration range relevant to workroom air, the National Institute for Occupational Safety and Health recommends that calibration be carried out using commercially available cylinders of hydrogen sulfide in dry nitrogen (NIOSH, 1977).

### 2.3.2 Gas chromatography with flame photometric detection

An Intersociety Committee method also exists for the determination of hydrogen sulfide using gas chromatography (Intersociety Committee, 1977b). This method requires the use of a gas chromatograph equipped with a flame photometric detector. A narrow-band optical filter selects the 394 ± 5 mm sulfur line. Gas chromatography separates sulfur compounds of low relative molecular mass before detection, and thereby allows individual quantitative measurement of sulfur-containing gases such as hydrogen sulfide, sulfur dioxide, methyl mercaptan, and dimethyl sulfide.

In situations where minimal quantities of reduced sulfur compounds other than hydrogen sulfide are present, flame photometry can be used directly, in which case the hydrogen sulfide concentration is approximately the same as the total sulfur compounds measured. An absorbant is usually required to selectively remove

sulfur dioxide, when flame photometry is used without separation of individual compounds by gas chromatography before detection.

The limits of detection of this method, at twice the noise level for hydrogen sulfide, sulfur dioxide, methyl mercaptan, and dimethyl sulfide, range from 0.005 to 0.013 mg/m³ (0.0035—0.009 ppm). Sensitivity can be increased by the use of sample concentration techniques such as a freeze-out loop in the gas chromatograph sampling line. The upper limit of detection is 0.5 mg/m³ (0.35 ppm) but it can be extended by sample dilution to higher ranges, if necessary. Although no data are available on the precision and accuracy of the method for atmospheric samples, repetitive sampling of standard reference gases containing a hydrogen sulfide concentration of 0.08 mg/m³ (0.055 ppm) and a sulfur dioxide concentration of 0.104 mg/m³ (0.036 ppm) gave a relative standard deviation of less than 3% of the amount present (Intersociety Committee, 1977b).

An advantage of flame photometric detection is that chemical solutions are not necessary, and the only required reagent is hydrogen for the flame. However, the need for a compressed hydrogen supply may be a disadvantage in certain situations. The analyser is calibrated using hydrogen sulfide, sulfur dioxide, methyl mercaptan, and dimethyl sulfide permeation tubes, and a dual-flow gas dilution device capable of producing reference standard atmospheres as low as the limits of detection of the method. Because the photomultiplier tube output is logarithmically proportional to the sulfur concentration, conversion can be done by either plotting the response against concentration on a logarithmic scale or by using a logarithmic-linear amplifier. Using either of these techniques, the range has been established at approximately 0.13—0.5 mg/m³ (0.09—0.35 ppm) with a 1% noise level (Intersociety Committee, 1977b).

Several commercial flame photometric detection analysers are now available (with and without separation of the sulfur compounds by gas chromatography before detection). This method of analysis for hydrogen sulfide is suitable for use as a laboratory method for calibration purposes or for continuous monitoring in stationary field settings.

### 2.3.3 Automatic monitors in stationary field settings

Paper tapes impregnated with lead acetate have been widely used for making measurements in the field (Denmead, 1962; Thom & Douglas, 1976; Institute of Hygiene and Epidemiology, 1978). A measured volume of air is filtered through the tape and the optical density of the discoloured area is compared with an unexposed area of the same tape. Numerous criticisms of these procedures have been reported and it is clear that the presence of any substance

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capable of oxidizing the lead sulfide can lead to substantial errors (Sanderson et al., 1966). Various modifications of the basic method have been suggested to minimize errors and increase sensitivity by Siu et al. (1971), including the substitution of mercuric chloride for lead acetate as proposed by Paré (1966). Natusch et al. (1974) evaluated various paper tape methods and concluded that tapes impregnated with silver nitrate are highly suitable for the determination of hydrogen sulfide concentrations in the range of 0.0015—75 mg/m³ (0.001—50 ppm). Moreover, they state that monitors using silver nitrate tape are simple, specific, portable, capable of unattended operation and inexpensive. However, silver nitrate tape systems remain subject to photodecomposition, an important deficiency for many field uses.

Continuous monitors based on various wet chemical procedures have been developed. For example, some sulfur dioxide monitors based on amperometric principles can be used to monitor hydrogen sulfide by replacing a silver screen (which normally filters out $H_2S$) with a barium acetate scrubber that removes any sulfur dioxide in the influent airstream. These devices are reported to have good maintenance characteristics and are suitable for use in remote areas. However, like most continuous instruments based on wet chemistry, they are relatively expensive (Lawrence Berkeley Laboratory, 1976).

Continuous monitors using the methylene blue method have also been developed (Levaggi et al., 1972). These units are attractive in that they possess the inherent sensitivity of the methylene blue method, but they require sophisticated support facilities and highly trained personnel for reliable operation. In this respect, the newer metal oxide-coated-chip semiconductor devices appear promising for field use. However, there are few published reports of field experience to date (Thompkins & Becker, 1976).

### 2.3.4 Direct-reading portable detection systems

Semiquantitative methods of hydrogen sulfide detection based on lead acetate-treated papers on tiles have been reported and are said to be sensitive to levels of about 1 mg/m³ (0.7 ppm) (Gilardi & Manganelli, 1963). However, long-duration detector tubes for hydrogen sulfide, suitable for use in the occupational environment, are now available, which are inexpensive and responsive over a wide range of concentrations (1—84 mg/m³; 0.7—56 ppm) and overcome some of the deficiencies of the lead acetate detectors (Leichnitz, 1977). The US National Institute for Occupational Safety and Health has investigated the quality and reproducibility of detector tubes available from various US manufacturers and reports that it is possible to obtain tubes that meet the quality specifications of the Institute (Johnson, 1972). Detector tubes for hydrogen sulfide are susceptible to interference from other sulfides, sulfur dioxide, and

nitrogen dioxide, but, generally such interference would result in false positive readings.

Various portable direct-reading hydrogen sulfide meters available on the US market have been evaluated by the National Institute for Occupational Safety and Health (Thompkins & Becker, 1976). These instruments are intended principally for industrial hygiene surveys and, in particular, for ascertaining the degree of general compliance with occupational health standards for hydrogen sulfide. The instruments surveyed operated on solid-state electrochemical principles, wet electrochemical principles, and in one case, on a photoionization principle. In terms of response time, calibration stability, and reliability, the photoionization instrument was regarded as superior, but it was the least specific of the instruments evaluated. The solid-state instruments tended to have slow response times and accuracy deficiencies but were very reliable and rugged. The wet electrochemical meters ranked highly in terms of accuracy, response time, and calibration stability but were somewhat less reliable.

### 2.3.5 Manual collection and analysis of air samples in occupational settings

In 1943, the American Public Health Association Sub-Committee on Chemical Methods in Air Analysis recommended collecting hydrogen sulfide with cadmium chloride in 2 simple petticoat bubblers in series followed by titration with iodine, using starch as an indicator or using an excess of iodine and back-titrating with sodium thiosulfate solution (Goldman et al., 1943). In 1965, the AIHA Analytical Guide (AIHA, 1965) listed 3 methods for determining hydrogen sulfide in air: *(a)* iodine oxidation using a Tutweiler buret; *(b)* cadmium sulfate and iodine in a midget impinger; and *(c)* formation of cadmium sulfide colloid using 2 midget impingers in series followed by conversion to methylene blue. The iodine methods are susceptible to interference at hydrogen sulfide levels expected in occupational settings. More recently, to ascertain employee exposure to hydrogen sulfide, the National Institute for Occupational Safety and Health recommended the collection of breathing-zone samples with a midget impinger and analysis by the methylene blue method (NIOSH, 1977).

In recent years, there have been developments in the use of solid adsorbents for the collection of sulfur gases. This technique for sample collection could be used in association with the gas chromatography using flame photometric detection for the measurement of hydrogen sulfide and other low relative molecular mass or self-containing gases (Black et al., 1978). This could ultimately lead to the development of solid-state personal dosimeters for hydrogen sulfide as an alternative to those that involve wet chemistry.

## 3. SOURCES OF HYDROGEN SULFIDE

### 3.1 Natural Sources

Hydrogen sulfide is one of the principal compounds involved in the natural sulfur cycle in the environment (National Research Council, USA, 1979). As indicated in Fig. 1, it occurs in volcanic gases

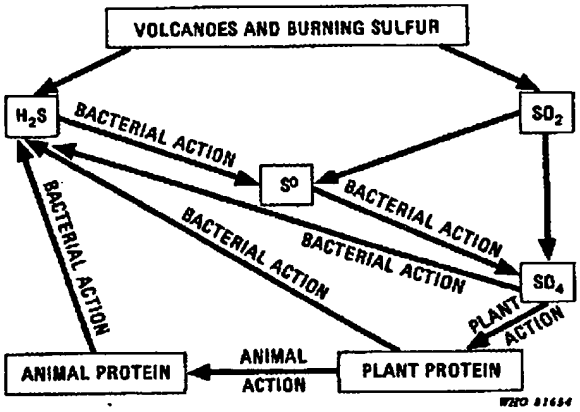


Fig. 1. The sulfur cycle (From: Cooper et al., 1976).

and is produced by bacterial action during the decay of both plant and animal protein (Cooper et al., 1976). Many bacteria, fungi, and actinomycetes release hydrogen sulfide into the environment during the decay of compounds containing sulfur-bearing amino acids and in the direct reduction of sulfate. The heterotroph *Proteus vulgaris* is an example of a common bacterium that produces hydrogen sulfide, when grown in the presence of protein (National Research Council, USA, 1979).

The reduction of sulfate to hydrogen sulfide can be accomplished by members of 2 genera of anaerobic bacteria, *Desulfovibrio* and *Desulfotomaculum*. The organic substrates for these organisms are usually short chain organic acids that are provided by the fermentative activities of other anaerobic bacteria or more complex organic material. Hence, hydrogen sulfide production can be expected in conditions where oxygen is depleted, organic material is present, and sulfate is available (National Research Council, USA, 1979).

From a microbiological point of view, the production of hydrogen sulfide is balanced by processes involving a variety of bacteria, found in soil and water, that can oxidize hydrogen sulfide to elemental

sulfur. Among these are the filamentous bacteria, *Beggiatoa* and *Thiothrix*. Photosynthetic bacteria belonging to the families Chromatiaceae and Chlorobiaceae oxidize hydrogen sulfide to elemental sulfur and sulfate in the presence of light and the absence of oxygen. Reduced sulfur compounds are also oxidized in nature by members of the genus *Thiobacillus*. The end result of this oxidative activity is the production of sulfate which, once formed, is extremely stable to further chemical activity in nature (National Research Council, USA, 1979).

As a result of these various biogeochemical processes, hydrogen sulfide occurs in and around sulfur springs and lakes and is almost continuously present as an air contaminant in some geothermally active areas.

### 3.2 Sources Associated with Human Activity

There are various circumstances under which naturally occurring hydrogen sulfide is released by human activity. For example, hydrogen sulfide occurring in association with natural gas and/or crude oil deposits in some areas may be released during extraction and drilling operations. The sulfur content of crude oils ranges from 0 to 5% and some natural gas deposits have been reported to comprise up to 42% hydrogen sulfide (Espach, 1950). Coals can contain sulfur levels of up to 80g/kg and, occasionally, conditions arise in which hydrogen sulfide is formed within such deposits. Thus, special precautions must be taken in some mining operations as well as in the drilling and extraction of natural gas and crude oils with significant sulfur content.

Hydrogen sulfide can also be released by activities surrounding the development and use of geothermal resources. At the Cerro Prieto geothermal power generating plant in Baja California, Mexico, for example, hydrogen sulfide levels are sufficiently high to necessitate special ventilation to protect electrical systems, and alarms for the protection of personnel (Mercado, 1975).

During industrial operations, hydrogen sulfide can be formed whenever elemental sulfur or certain sulfur-containing compounds come into contact with organic materals at high temperatures. It is usually produced as an undesirable by-product, though it is also used as an important reagent or desirable intermediate compound in some industrial processes such as the manufacture of sulfides, sodium hydrosulfide, and various organic sulfur compounds. Examples of processes in which hydrogen sulfide occurs as a by-product include the production of coke from sulfur-containing coal, the production of carbon disulfide, the manufacture of viscose rayon in the Kraft process for producing wood pulp (Macaluso, 1969) and sulfur extraction by the Frasch process.

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In refining sulfur-containing crude oils, about 80%—90% of the divalent sulfur compounds of hydrogen and carbon are converted to hydrogen sulfide. Both the hydrogen sulfide produced and that occurring in other industrial, geothermal, or natural gas streams can be recovered by one of a number of processes that can be classified as either absorption-desorption processes or processes involving oxidation to oxides or to elemental sulfur. The bulk of hydrogen sulfide recovered in industrial processes is used to produce elemental sulfur or sulfuric acid (Macaluso, 1969).

Large quantities of hydrogen sulfide are used in the production of heavy water, which is employed as a moderator in some nuclear power reactors. The process is based on enrichment of the deuterium content of water by hydrogen sulfide in a gas/liquid ion exchange system, followed by separation of heavy water and water by fractional distillation (McGraw-Hill Encyclopedia of Science and Technology, 1960).

In the tanning industry, hydrogen sulfide is produced in the process by which hair or wool is removed from the hides. This typically involves deliming by adding ammonium chloride or ammonium sulfate followed by pickling with sulfuric acid, and takes place in large rotating drums. The gases evolved, including hydrogen sulfide, are released from the drums on opening the hatches either to add chemicals or to unload the treated hides, and also from the waste waters (ILO, 1971).

As in the natural environment, hydrogen sulfide can be generated by bacterial action in industrial or community settings in malodorous and sometimes dangerous amounts.

In some countries, such as India and Sri Lanka, hydrogen sulfide is produced in the process by which coconut fibres are separated from the husk. This procedure involves the decomposition of the husks in shallow ponds. The hydrogen sulfide is produced as a result of microbiological decay processes.

## 4. ENVIRONMENTAL LEVELS AND EXPOSURE

### 4.1 Concentrations in Outdoor Air

There are few published data on either natural background or urban air levels of hydrogen sulfide. Robinson & Robbins (1970) estimated the average ambient air level of hydrogen sulfide to be 0.0003 mg/m$^3$ (0.0002 ppm). This estimate supports the data of Minster (1963) who, when sampling over a 2½-year period in northwest London, reported that air levels of hydrogen sulfide were generally below 0.00015 mg/m$^3$ (0.0001 ppm), under clear, fresh conditions. Minster (1963) also reported that average summer levels ranged from 0.00015 to 0.0007 mg/m$^3$ (0.0001—0.0005 ppm) and average winter

levels from 0.0007 to 0.0015 mg/m³ (0.0005—0.001 ppm). Data collected from this same station during the London fog of December 1962 indicated a hydrogen sulfide concentration of up to 0.046 mg/m³ (0.033 ppm) on 6 December during heavy fog (each sampling time was 32 min).

Measurements summarized by the US National Air Pollution Control Administration show concentrations ranging from below 0.001 mg/m³ to 0.006 mg/m³ (0.0007 to 0.0042 ppm) at various urban locations in the USA in the period 1951—64 (Miner, 1969). However, as sensitive and standardized methods of sampling and analysis for hydrogen sulfide were lacking during this period, there is some doubt about the reliability of these data. Furthermore, the averaging times for the data are not available.

Much higher concentrations of hydrogen sulfide have been measured near point sources. In California, peak concentrations as high as 0.20 mg/m³ (0.13 ppm) were measured near a pulp and papermill at the time of its commissioning (California Air Resources Board, 1970). After operating for several months, levels fell to 0.015 mg/m³ (0.010 ppm) or less. The averaging time was not reported. Near a brick works in Boom, Belgium, air levels of hydrogen sulfide were monitored over a 6-month period. During this time, the average 24-h concentration of hydrogen sulfide was 0.005 mg/m³ (0.003 ppm) with occasional daily averages in excess of 0.017 mg/m³ (0.011 ppm) (Institute of Hygiene & Epidemiology, 1978).

A major accidental release of hydrogen sulfide occurred at Poza Rica, Mexico, in 1950 (McCabe & Clayton, 1952). Although no data could be collected on environmental levels during this episode, numerous fatalities occurred indicating that exposure levels were most likely in excess of 1500—3000 mg/m³ (1000—2000 ppm). Further details of this episode are given in section 6.3.

In the geothermally active areas in and around the city of Rotorua, New Zealand, airborne concentrations of hydrogen sulfide are usually sufficient to cause noticeable odours (Thom & Douglas, 1976). At one site, for one day, a 1-h mean concentration of up to 2.0 mg/m³ (1.4 ppm) was reported (Thom & Douglas, 1976). Continuous measurements taken at another site over a period of 5 months showed that a concentration of 0.08 mg/m³ (0.05 ppm) was exceeded, on average, 35% of the time. It was also found that there were considerable seasonal variations in the hydrogen sulfide levels, reflecting the fluctuating steam-use patterns and also changes in the dispersive nature of the atmosphere. During the mid-winter months of the 1978 monitoring period, a concentration of hydrogen sulfide in air of 0.08 mg/m³ (0.05 ppm) was exceeded more than 55% of the time, whereas, during warmer months, this concentration was exceeded less than 20% of the time (Rolfe, 1980).

Also in New Zealand, the discharge of industrial and domestic liquid wastes into an inlet near Auckland created conditions in which

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### 4.2 Concentrations in Work Places

Under normal operating conditions, concentrations of hydrogen sulfide in the air in work places are believed to be less than 10–15 mg/m³ (7–10 ppm), the 8-h time weighted average that most national authorities have set as their occupational exposure standard (Annex).

It is well known, however, that hazardous exposures to hydrogen sulfide can occur under accidental circumstances in industries in which gas streams with a high hydrogen sulfide content exist. Furthermore, as hydrogen sulfide is slightly heavier than air, it can accumulate in toxic concentrations in low-lying areas, even when generated or leaking at very low rates. However, in such cases, the environmental levels of hydrogen sulfide have usually only been measured after the accidents in question, or have been determined by simulation or reenactment. Concentrations that have been reported range from 150 mg/m³ (100 ppm), in which a worker lost consciousness while sawing ebonite boards (Brown, 1969), to 18 000 mg/m³ (12 000 ppm) in a case in which a truck driver died while cleaning the tank of a vehicle used to transport industrial waste (Simson & Simpson, 1971). In an outdoor setting, 4 workmen lost consciousness while digging a pit in marshy land in which hydrogen sulfide concentrations in air of 442–810 mg/m³ (295–540 ppm) were measured 5 days later (Anonymous, 1952). Alexander (1974) reported hydrogen sulfide concentrations as high as 0.037 mg/litre (24.8 ppm) in a sewage stabilization pond and 10.0–13.2 mg/m³ (6.7–8.8 ppm) in the air 15 m from this pond. In a report by Ahlborg (1951) on hydrogen sulfide poisoning in the Swedish shale oil industry, concentrations of hydrogen sulfide measured at various locations in the plant ranged from 30 to 900 mg/m³ (20–600 ppm), though men seldom worked where the high levels occurred.

More recently, the US National Institute for Occupational Safety and Health reported that, in viscose rayon churn rooms, spinning tanks, and drying and storage cells, workers were mainly exposed during the working day to hydrogen sulfide concentrations of 23 mg/m³ (15 ppm) or less with occasional peaks of 150 mg/m³ (100 ppm) (NIOSH, 1977).

In the USA, it has been estimated that there are 125 000 employees potentially exposed to hydrogen sulfide (NIOSH, 1977). Table 1 is a list of occupations in which such exposure can occur

ranging according to occupation from rare exposure to low concentrations, to frequent exposure to concentrations very near those associated with adverse health effects.

Table 1. Examples of occupations with potential exposure to hydrogen sulfide[a]

| | |
|---|---|
| Animal fat and oil processors | Lithographers |
| Animal manure removers | Lithopone makers |
| Artificial-flavour makers | Livestock farmers |
| Asphalt storage workers | Manhole and trench workers |
| Barium carbonate makers | Metallurgists |
| Barium salt makers | Miners |
| Blast furnace workers | Natural gas production and processing workers |
| Brewery workers | Painters using polysulfide caulking compounds |
| Bromide-brine workers | Papermakers |
| Cable splicers | Petroleum production and refinery workers |
| Caisson workers | Phosphate purifiers |
| Carbon disulfide makers | Photo-engravers |
| Cellophane makers | Pipeline maintenance workers |
| Chemical laboratory workers, teachers, students | Pyrite burners |
| Cistern cleaners | Rayon makers |
| Citrus root fumigators | Refrigerant makers |
| Coal gasification workers | Rubber and plastics processors |
| Coke oven workers | Septic tank cleaners |
| Copper-ore sulfidizers | Sewage treatment plant workers |
| Depilatory makers | Sewer workers |
| Dyemakers | Sheepdippers |
| Excavators | Silk makers |
| Felt makers | Slaughterhouse workers |
| Fermentation process workers | Smelting workers |
| Fertilizer makers | Soapmakers |
| Fishing and fish-processing workers | Sugar beet and cane processors |
| Fur dressers | Sulfur spa workers |
| Geothermal-power drilling and production workers | Sulfur products processors |
| Gluemakers | Synthetic-fibre makers |
| Gold-ore workers | Tank gaugers |
| Heavy-metal precipitators | Tannery workers |
| Heavy-water manufacturers | Textile printers |
| Hydrochloric acid purifiers | Thiophene makers |
| Hydrogen sulfide production and sales workers | Tunnel workers |
| Landfill workers | Well diggers and cleaners |
| Lead ore sulfidizers | Wool pullers |
| Lead removers | |

[a] From: NIOSH (1977).

## 5. EFFECTS ON EXPERIMENTAL ANIMALS

Very little information is available on the effects of low level concentrations of hydrogen sulfide gas on experimental animals; most published data have emphasized the effects of exposure to lethal or near-lethal concentrations of the gas. According to Evans

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(1967) and Smith & Gosselin (1979), the effects of high doses of hydrogen sulfide and high doses of cyanide are very similar. Both inhibit the enzyme cytochrome c oxidase [EC 1.9.3.1]. This was demonstrated in studies using purified preparations of the enzyme (Smith & Gosselin, 1979).

When sodium sulfide at 0.1, 0.25, and 0.32 mmol/kg body weight was administered intraperitoneally to mice, sulfide was not exhaled (Susman et al., 1978) suggesting that it was inactivated primarily by metabolism. In studies on the inhalation of hydrogen sulfide in rats, cats, rabbits, and dogs, the nervous centres were first excited and then paralysed; pupils first contracted and then dilated; blood pressure was first raised, then lowered; and respiration first increased and then halted (Evans, 1967; Haggard, 1925). The findings of Lehmann (1892) in the cat, dog, and rabbit, of Haggard (1925) in the dog, and of Sayers et al. (1925) in the canary, rat, guineapig, dog, and goat, are quite consistent: at 150—225 mg/m³ (100—150 ppm), signs of local irritation of eyes and throat after many hours of exposure; at 300—450 mg/m³ (200—300 ppm), eye and mucous membrane irritation after inhalation for 1 h and slight general effects with prolonged inhalation; at 750—1050 mg/m³ (500—700 ppm), local irritation and slight systemic symptoms in less than 1 h and possible death after several hours' exposure; at 1350 mg/m³ (900 ppm), grave systemic effects within 30 min and death in less than 1 h; at 2250 mg/m³ (1500 ppm), collapse and death within 15—30 min; and at 2700 mg/m³ (1800 ppm), immediate collapse, respiratory paralysis, and death.

When mice were exposed repeatedly (4 times for 2 h, at 4-day intervals) to a hydrogen sulfide concentration in air of 150 mg/m³ (100 ppm), the critical inhibition of terminal cytochrome c oxidase appeared to be cumulative. This effect was accompanied by a cumulative decrease in cerebral RNA synthesis (Savolainen et al., 1980). Experimental studies on rabbits indicated that either a single or repeated exposure for 1.5 h per day (5 consecutive days) to a hydrogen sulfide concentration in air of 105 mg/m³ (70 ppm) caused electrocardiographic (ECG) changes (Kósmider et al., 1967).

Though some small differences in susceptibility to hydrogen sulfide gas were exhibited among the species studied by Sayers et al., (1925), canaries being the most sensitive and goats the most resistant, the interspecies differences were slight. It is agreed among investigators that the effects of hydrogen sulfide gas on the nervous system represent the most important aspect of its toxicity (Haggard, 1925; Evans, 1967). Beck et al. (1979) showed that ethanol in doses of 0.33—0.66 g/kg significantly shortened the time to loss of consciousness in rats exposed to a hydrogen sulfide concentration in air of 1200 mg/m³ (800 ppm) for 30 min. The induction of methaemoglobinaemia by the injection of sodium nitrite had both protective and antidotal effects against hydrogen sulfide poisoning in mice, armadillos, rabbits, and dogs (Smith & Gosselin, 1979).

Water containing a hydrogen sulfide concentration as low as 0.86 mg/litre was toxic to trout after exposure for 24 h (McKee & Wolf, 1971).

## 6. EFFECTS ON MAN

Adequate systematic studies of the relationship between hydrogen sulfide exposure and health status in the general population have not been carried out. Controlled exposure of human subjects to concentrations of hydrogen sulfide gas exceeding about 75 mg/m³ (50 ppm) has been deemed to involve excessive risk because of the possibility of injury to the lungs (Sayers et al., 1925; National Research Council, USA, 1979). Furthermore, except for studies related to odour threshold, controlled exposures of human subjects to very low concentrations of the gas, for example, below 1.5 mg/m³ (1.0 ppm) have not been reported. Thus, the information presented in this section has mainly been derived from reports of accidental and industrial exposures to hydrogen sulfide. A general discussion of the toxicology of hydrogen sulfide has been included, because a basic understanding of the subject is necessary for a discussion of the role of the gas as an industrial and community hazard.

### 6.1 General Toxicological Considerations

The following observations have been derived from reports of studies involving man. However, for clarification, some studies on experimental animals have also been included. In general, both animals and man respond in a very similar fashion to toxic concentrations of hydrogen sulfide. It is both an irritant and an asphyxiant gas (Table 2) that induces local inflammation of the membranes of the human eye and respiratory tract (Yant, 1930). It has been shown that eye irritation, the most commonly reported effect of hydrogen sulfide exposure, can occur after several hours' exposure to concentrations of 16—32 mg/m³ (10.5—21.0 ppm) (Elkins, 1939; Nesswetha, 1969). However, pulmonary tract irritation is, potentially, a more serious reaction. When inhaled by dogs, hydrogen sulfide exerted an irritant action through the entire respiratory tract, though the deeper structures suffered the greatest damage

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Exposure to hydrogen sulfide gas did not induce important effects on the human skin nor was any appreciable absorption through intact skin observed (Yant, 1930). However, Petrun (1966) reported that when the skin of rabbits was exposed to hydrogen sulfide at concentrations of 1050 and 2100 mg/m³ (700 and 1400 ppm), trace amounts of hydrogen sulfide were found in the exhaled air of the rabbits. No quantitative information was given.

Hydrogen sulfide gas is rapidly absorbed through the lung. Like hydrogen cyanide, it is a potent inhibitor of cytochrome c oxidase that interferes with tissue use (Smith & Gosselin, 1979). As a result, the oxidative metabolism may slow to the point where tissue metabolic demands cannot be met. In the central nervous system, the result may be paralysis of the respiratory centres. Respiratory arrest and death from asphyxia would be the natural outcome.

In studies on dogs (Haggard, 1925), hydrogen sulfide at concentrations of 1500—3000 mg/m³ (1000—2000 ppm) initially stimulated excessively rapid breathing (hyperpnoea), because of a depletion in the carbon dioxide content of the blood (hypocapnia). This was followed by a period of respiratory inactivity (apnoea). Spontaneous respiration may be reestablished, if carbon dioxide depletion has not progressed beyond the point where prompt reaccumulation can act as a stimulus to the reestablishment of respiration. If spontaneous recovery does not occur and artificial respiration is not applied rapidly, death from asphyxia is the inevitable result (Haggard, 1925). At about 2250 mg/m³ (1500 ppm), the sequence of events in the dog was the same, except that the reaction was more pronounced; at 3000 mg/m³ (2000 ppm) there was respiratory paralysis after a breath or two and, in Haggard's words, "the victim falls to the ground as though struck down". When breathing ceases, generalized convulsions frequently begin. There appears to be no clear explanation of the cause of this picture of sudden collapse. According to Haggard (1925), this form of respiratory failure is not related to the carbon dioxide content of the blood but, rather, to the directly paralysing effect of hydrogen sulfide on the respiratory centre. Breathing is never reestablished spontaneously following this hydrogen sulfide-induced respiratory paralysis. Haggard noted, however, that because the heart continues to beat for several minutes after respiration has ceased, death from asphyxia can be prevented if artificial respiration is begun immediately and is continued until the hydrogen sulfide concentration in the blood decreases. This decrease is probably a consequence of metabolic processes, as shown in mice by Susman et al. (1978) rather than, as once believed, the result of the pulmonary excretion of the gas.

Smith & Gosselin (1979) have called attention to the confusion that exists in the literature with regard to the effects of hydrogen

sulfide on haemoglobin. They emphasize that many studies have proved that neither sulfhaemoglobin nor any other abnormal pigments are present in significant concentrations in the blood of animals or human subjects, fatally poisoned by hydrogen sulfide.

The characteristic "rotten egg" odour of hydrogen sulfide is an important aspect of the toxicology of the gas. The threshold of perception (odour) varies considerably depending on individual sensitivity. Several authors have reported odour detection thresholds ranging from 0.0007 mg/m³ to 0.20 mg/m³ (0.0005—0.13 ppm) (Table 2). Thus, the odour of hydrogen sulfide gas can be a very sensitive indicator of its presence in low concentrations. However, at higher concentrations (> 225 mg/m³ (150 ppm)), hydrogen sulfide exerts a paralysing effect on the olfactory apparatus (Milby, 1962), thus neutralizing the value of its odour as a warning signal. Poda (1966) reported that among 42 workers, who were rendered unconscious from overexposure to hydrogen sulfide, the majority did not smell the charaoteristic odour of the gas but noted a sickeningly sweet odour, very briefly, before losing consciousness.

Table 2. Effects of hydrogen sulfide exposure at various concentrations in air

| Effect | Concentration | | Duration of exposure | Reference |
|---|---|---|---|---|
| | mg/m³ | ppm | | |
| Man | | | | |
| Approximate threshold for odour | 0.0007—0.2 | 0.0005—0.13 | A few seconds to less than 1 min | Yant (1930); Ryazanov (1962); Adams & Young (1968); Leonardos et al. (1969); Lindvall (1970); Thiele (1979); Winneke et al. (1979) |
| Threshold of eye irritation | 16—32 | 10.5—21 | 6—7 h | Elkins (1939) Nesswetha (1969) |
| Acute conjuctivitis (gas eye) | 75—150 | 50—100 | > 1 h | Yant (1930) |
| Loss of sense of smell | 225—300 | 150—200 | 2—15 min | Sayers et al. (1925) |
| Animals[a] | | | | |
| Local irritation and slight systemic symptoms; possible death after several hours | 750—1050 | 500—700 | < 1 h | Haggard (1925) |
| Systemic symptoms; death in less than 1 h | 1350 | 900 | < 30 min | Haggard (1925) |
| Death | 2250 | 1500 | 15—30 min | Haggard (1925) |

[a] These observations were made in experimental animals. However, there are no better quantitative data available concerning man with respect to exposure to hydrogen sulfide at high concentrations.

Hydrogen sulfide intoxication in man has generally been categorized according to 3 clinical forms, acute, subacute, and chronic, depending on the nature of the predominant clinical signs and

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symptoms (National Research Council, USA, 1979). The term "acute hydrogen sulfide intoxication" has been most often used to describe systemic poisoning characterized by rapid onset and predominance of signs and symptoms of nervous system involvement. The term "subacute intoxication" has been applied to episodes of poisoning in which signs and symptoms of eye and respiratory tract irritation were most prominent. "Chronic hydrogen sulfide intoxication" has been applied by some authors to describe a prolonged state of symptoms resulting from a single or repeated exposure to concentrations of hydrogen sulfide that do not produce clear-cut manifestations of either acute or subacute illness.

In a document prepared by the National Research Council of the National Academy of Sciences of the USA (National Research Council, USA, 1979), the observation was made that application of the terms "acute", "subacute" and "chronic" to hydrogen sulfide exposure was both imprecise and misleading. However, rather than abandon these frequently used terms altogether, the authors suggested a series of clarifying definitions which are quoted in the following paragraphs, and will henceforth be used in this section.

"*Acute intoxication:* Effects of a single exposure [seconds- minutes] [a] to massive concentrations of hydrogen sulfide that rapidly produce signs of respiratory distress. Concentrations approximating 1400 mg/m³ (1000 ppm) are usually required to cause acute intoxication.

*Sub-acute intoxication:* Effects of continuous exposure [up to several hours] [a] to mid-level 140 to 1400 mg/m³ (100 to 1000 ppm) concentrations of hydrogen sulfide. Eye irritation (gas eye) is the most commonly reported effect, but pulmonary edema (in the absence of acute intoxication) has also been noted.

*Chronic intoxication:* Effects of intermittent exposures to low to intermediate concentrations 70 to 140 mg/m³ (50 to 100 ppm) of hydrogen sulfide, characterized by "lingering", largely subjective manifestations of illness."

It is important to note that these definitions do not include a consideration of the health consequences to man associated with prolonged low-level exposure to hydrogen sulfide gas, such as may be encountered under conditions of general urban air pollution.

A concentration of hydrogen sulfide in drinking water as low as 0.07 μg/litre (0.05 ppm) can affect its taste (Campbell et al., 1958).

### 6.2 Occupational Exposure

In certain occupations, workers are intermittently exposed to concentrations of hydrogen sulfide that are not only malodorous but

[a] Time factors added by WHO Task Group.

can, in some situations, cause severe adverse health effects and even death. Usually, hydrogen sulfide is encountered in the workplace as an undesirable by-product of a manufacturing process, notably petroleum refining, viscose rayon production, sugar beet processing, and tannery work (Milby, 1962; NIOSH, 1977). In other occupations, for example cesspool cleaning and work in sewers, exposure to hydrogen sulfide may occur when the gas is formed as a result of the decomposition of sulfur-containing organic matter, in the absence of complete oxidation. Deaths attributed to such exposure occurred in the sewers of Paris in the 1780s (Mitchell & Davenport, 1924) and still occur under various circumstances.

Workers in certain occupations risk exposure to naturally occurring hydrogen sulfide; geothermal energy workers and spa attendants may be included in this category.

Acute hydrogen sulfide intoxication is a dramatic, often fatal event. Three men were inadvertently enveloped in a cloud of hydrogen sulfide gas escaping from a cylinder under high pressure; all fell, as if struck down, and ceased breathing. Only as a result of prompt resuscitation by trained onlookers did the men survive, though the two most seriously affected experienced violent convulsions and did not recover consciousness for some 30 min. None of the men suffered important after-effects, and none recalled having noted the characteristic odour of hydrogen sulfide. The hydrogen sulfide concentrations to which the men were exposed were estimated to be about 2800 mg/m³ (2000 ppm) (Milby, 1962). Twelve workmen in a plant that produced benzyl polysulfide were overcome by hydrogen sulfide gas, when a pipe used to transfer sodium sulfhydrate ruptured. The liquid sulfhydrate drained into a nearby sewer, where it reacted with acid sewage releasing hydrogen sulfide from several sewer openings in the immediate vicinity. Two of the 12 workmen died, probably as a result of respiratory arrest; 3 stopped breathing but were successfully resuscitated; 6 lost consciousness but recovered spontaneously, and 1 individual developed pulmonary oedema that responded to therapy (Kleinfeld et al., 1964).

Burnett et al. (1977) reviewed 221 cases of exposure to hydrogen sulfide associated with the oil, gas, and petrochemical industries in Canada. The overall mortality was 6%; three-quarters of all victims experienced a period of unconsciousness and 12% were comatose. A high proportion of patients had other neurological signs and symptoms, including altered behaviour patterns, confusion, vertigo, agitation, or somnolence. Respiratory tract effects were second in frequency only to neurological manifestations. Forty percent of all cases required some form of respiratory assistance and 15% of all cases developed pulmonary oedema. Less severely affected patients complained primarily of headaches, sore eyes, or gastrointestinal upsets. There were no recognizable sequelae among the survivors. Data on environmental exposure levels were not reported.

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Nearly fatal cases of acute hydrogen sulfide intoxication associated with sequelae of varying severity have been reported. A 48-year-old farmer, who collapsed from hydrogen sulfide intoxication while shovelling manure, continued to have convulsive seizures after resuscitation. The ECG changes suggested myocardial infarction. The patient recovered but a slight, persistent dizziness remained (Kaipainen, 1954). A 46-year-old sewer worker, who was overcome by hydrogen sulfide in a manhole for 30 min, was cyanotic, suffering generalized spasms, and required artificial respiration. A week later, he could move and speak only with great effort; a month afterwards, he still exhibited neurological deficits. The ECG showed evidence of small anterolateral infarct and a right bundle branch block. Three months later, although ambulatory, the patient still suffered from anginal pain upon exertion (Hurwitz & Taylor, 1954). In a man who had suffered severe hydrogen sulfide intoxication with collapse and respiratory failure, ECG evidence of myocardial ischaemia was noted during the early phase of acute illness but gradually disappeared over a period of 15 days (Kemper, 1966). Each of these 3 events, in which sequelae were reported, were characterized by periods of unconsciousness during which hypoxia of vital tissues was likely to have occurred and may have been the basis for the observed prolonged effects. Many other instances of sequelae following acute hydrogen sulfide intoxication have been reported. Most resemble the cases just mentioned, in which serious poisoning with unconsciousness preceded the appearance of sequelae.

Ahlborg (1951) described 58 cases of acute hydrogen sulfide intoxication in Sweden's shale oil industry. There were no fatalities. Symptoms were generally uniform: sudden fatigue, dizziness, and intense anxiety followed by unconsciousness with or without respiratory failure. Several cases of acute poisoning were not associated with unconsciousness, otherwise symptoms were similar to those of the other cases. The diagnosis of "sequelae after acute hydrogen sulfide poisoning" was made in 15 cases. The majority of these had a history of repeated acute intoxications followed in each case by neurasthenic problems (fatigue, somnolence, headache, lack of initiative, irritability, anxiety and poor memory, and decreased libido), though some developed sequelae following acute intoxication without an intercurrent episode of unconsciousness. Many stricken workers developed an increase in sensitivity (aversion) to the odour of gas of any type, even pure gasoline vapour (Ahlborg, 1951).

Numerous case histories of fatal hydrogen sulfide intoxication have been reported (Larson et al., 1964; Adelson & Sunshine, 1966; Simson & Simpson, 1971). Oedema of the lungs and brain are common post-mortem findings. The presence of detectable concentrations of hydrogen sulfide in the blood has been reported on several occasions (Larson et al., 1964; Adelson & Sunshine, 1966) and con-

centrations in the blood of fatally poisoned victims have ranged from 1.70 mg to 3.75 mg/litre (McAnalley et al., 1979).

In acute hydrogen sulfide intoxication, cessation of respiration is an immediate threat to life. Accordingly, the provision of artificially assisted respiration on an emergency basis is absolutely critical. There is some question as to whether mouth-to-mouth resuscitation may create a potential health hazard to the rescuer, because of the presence of hydrogen sulfide in the expired air or on the clothing of the victim. Thus, methods of artificial respiration requiring less direct contact (for example, back-pressure-arm lift) may be prudent.

### 6.3 General Population Exposure

There are several reports of episodes of general population response to air contamination by hydrogen sulfide. Information derived from these events is consistent with observations reported among workers occupationally exposed to hydrogen sulfide. Table 2 demonstrates the wide range of odour perception thresholds for hydrogen sulfide reported by various investigators. In view of the magnitude of these differences, it is not possible to state with certainty the concentration at which odour-related complaints can be expected.

A catastrophic exposure episode involving the release of large quantities of hydrogen sulfide into a small community was reported by McCabe & Clayton (1952). This occurred in 1950 in Poza Rica, Mexico, a city of 22 000 people located about 210 km northeast of Mexico City. Poza Rica was then the centre of Mexico's leading oil-producing district and the site of several oil field installations, including a sulfur-recovery plant. An early morning malfunction of the waste gas flare resulted in the release of large quantities of unburned hydrogen sulfide into the atmosphere. The unburned gas, aided by a low-level temperature inversion and light early morning breezes, was carried to a residential area adjacent to the plant area. Residents of the area were overcome while attempting to leave the area and while assisting stricken neighbours. Within 3 h, 320 persons were hospitalized and 22 died. The most frequent symptom was loss of the sense of smell. More than half of the patients lost consciousness, many suffered signs and symptoms of respiratory tract and eye irritation and 9 developed pulmonary oedema. Four of the 320 victims exhibited neurological sequelae; 2 experienced neuritis of the acoustic nerve; 1 developed dysarthria; the fourth patient suffered aggravation of pre-existing epilepsy. The duration of these neurological sequelae was not reported.

There have been reports of other episodes of general atmospheric pollution by hydrogen sulfide evolved from both natural and

industrial sources, but none has been as severe as the Poza Rica incident.

In the geothermal areas of Rotorua, New Zealand, a city of 40 000 people, steam and hot water from approximately 500 active bores are used to heat houses, buildings, and swimming pools, and to provide domestic hot water supplies and steam for cooking boxes.

In these areas, accidental fatal cases of acute hydrogen sulfide intoxication associated with improper ventilation of geothermal steam-heated dwellings have occasionally been reported. For example, at least 3 deaths from acute hydrogen sulfide poisoning occurred in 1962. However, with the introduction of legal requirements regarding the safe domestic use of the geothermal resources, and possibly also as a result of increased public awareness of the dangers involved, no fatalities attributable to hydrogen sulfide have occurred in Rotorua since 1962 (Thom & Douglas, 1976).

Air pollution monitoring for hydrogen sulfide has been conducted, during several periods over the past 15 years, at various sites in Rotorua. However, there has been considerable variation in the results obtained between the various sites, and furthermore, the concentrations measured showed considerable seasonal variations. Some of the results of these measurements are mentioned in section 4.1.

In 1964, the Division of Air Pollution, US Public Health Service, reported that in the city of Terre Haute, Indiana, biodegradation of industrial wastes in a 14.5-ha lagoon caused the atmospheric concentration of hydrogen sulfide to reach a 1-h mean concentration of 0.45 mg/m³ (0.3 ppm). As a result, 81 complaints were registered by the public, 41 of which were health-related. The most common complaints were concerned with the perception of a foul odour. The most common effects were nausea, interruption of sleep, burning of the eyes, and shortness of breath. Less common manifestations were cough, headache, and anorexia. Several acute asthma attacks were reported, but the association of these attacks with the hydrogen sulfide incident was not clearly established. Though no grave physical illnesses could be directly related to the air pollution incident, the investigators stressed that the odours emanating from the lagoon caused more than a mere nuisance (United States Public Health Service, 1964).

The Poza Rica tragedy provides ample evidence that the accidental release of hydrogen sulfide into a community can be expected to cause systemic intoxication of varying severity. The Rotorua experience is notable in that it emphasizes the fact that the potential for serious, even fatal, hydrogen sulfide intoxication is present in active geothermal areas. The more common picture of general population exposure is exemplified by the Terre Haute incident where an industry-related source of low-level concentrations of hydrogen

sulfide gas created a health problem which, although not grave, exceeded the level of mere nuisance.

The potential of long-term, low-level exposure to hydrogen sulfide to cause pulmonary changes of the type known to be associated with other irritant gases such as oxides of nitrogen and sulfur has scarcely been studied. No epidemiological data are available, at present, upon which to base any sound conclusions.

## 7. EVALUATION OF HEALTH RISKS TO MAN FROM EXPOSURE TO HYDROGEN SULFIDE

By far the most important recognized toxic effect of hydrogen sulfide is its ability to induce acute intoxication, characterized by immediate collapse, frequently accompanied by respiratory arrest and, without treatment, death. The scientific literature abounds with cases of this type, most often associated with industrial overexposure. However, a few cases of acute hydrogen sulfide exposure have been recorded in the general population as a result of the release of hydrogen sulfide either from an industrial process or from natural sources. A second form of injury associated with exposure to hydrogen sulfide is caused by the irritative action of the gas on the mucous membranes of the eyes and respiratory tract. Keratoconjunctivitis (gas eye) and pulmonary oedema are two most serious manifestations of this local irritative effect. The malodorous property of hydrogen sulfide gas is well recognized and this characteristic alone is believed by many to be capable of producing impairment of human health and well-being.

Most of the information available on human health effects associated with exposure to various concentrations of hydrogen sulfide gas has come from observations on accidental and industrial exposures. With the exception of the Poza Rica catastrophe, information on general population exposures and associated health effects is sketchy at best. There is also little information on controlled human exposure to hydrogen sulfide gas, and, except for data from odour threshold studies, the information that is available is more than 50 years old. Although a small amount of information is available on the effects on experimental animals of high concentrations of hydrogen sulfide gas, there is virtually no information on the long-term, low-level effects of the gas on experimental animals.

Furthermore, epidemiological data are lacking concerning the health consequences of long-term, low-level exposure to hydrogen sulfide, in both the general and industrial populations.

### 7.1 Exposure Levels

General population air pollution problems associated with hydrogen sulfide arise mainly in connexion with malodorous conditions, traceable to point sources. Such sources can be industrial or, in some cases, polluted bodies of water. Peak levels as high as 0.20 mg/m³ (0.13 ppm) have been reported in the air in the neighbourhood of industrial sources. Hydrogen sulfide is also a common pollutant in geothermally active areas. At one site in a geothermal area in New Zealand, where continuous measurements were carried out over a 5-month period, a level of 0.08 mg/m³ (0.05 ppm) was exceeded, on average, for 35% of the time.

Concentrations of hydrogen sulfide in the workplace also vary widely. In the shale-oil industry and in viscose rayon production, for example, maximum levels of exposure during the work day have been reported to range from 23 to 30 mg/m³ (15—20 ppm). In general, however, massive accidental exposure to hydrogen sulfide has constituted the principal hazard of this gas in industrial settings. In many cases, such exposure has occurred because of equipment breakage or malfunction. However, because hydrogen sulfide is heavier than air, it can accumulate in lethal concentrations in low-lying or enclosed areas. Numerous fatalities have occurred from the slow, insidious accumulation of the gas in the air in both ambient and industrial environments.

### 7.2 Experimental Animal Studies

The toxic effects of hydrogen sulfide gas have not been studied extensively in experimental animals. However, in studies on a number of animal species including the mouse, rat, cat, dog, and goat, it has been shown that the primary target of hydrogen sulfide in high doses is the nervous system. Collapse, followed by respiratory arrest and asphyxia resulting from the paralysing effects of high concentrations of hydrogen sulfide on the respiratory centres of the central nervous system, is the usual sequence of events leading to death.

Little information is available in the published literature concerning the effects in experimental animals of long-term, low-level exposure to hydrogen sulfide.

### 7.3 Effects of Occupational Exposure

Inadvertent and accidental exposure of human subjects to high concentrations of hydrogen sulfide has occurred among workers engaged in petroleum refining, viscose rayon production, sugar beet processing, and tannery work. Exposure levels have not been precisely documented in many of these situations. Reported effects range from the relatively less grave conditions of neurasthenic and oto-neurological symptoms and keratoconjunctivitis to the more serious effects of pulmonary oedema, respiratory failure, collapse, and even death. From the available data, it can be estimated that exposure for seconds or minutes to concentrations of approximately 1400 mg/m³ (1000 ppm) or more would cause acute intoxication, concentrations of 140—1400 mg/m³ (100—1000 ppm) with an exposure time of up to several hours would produce keratoconjunctivitis and pulmonary oedema, and intermittent exposures to concentrations of 70—140 mg/m³ (50—100 ppm) could be associated with lingering, largely subjective, manifestations believed by some to represent chronic intoxication. Various studies have associated exposure to hydrogen sulfide in concentrations as low as 16—32 mg/m³ (10.5—21.0 ppm) for several hours with eye irritation in workers.

Effects of low-level, long-term industrial exposure to hydrogen sulfide have not been systematically evaluated.

### 7.4. Effects of General Population Exposure

Several episodes of exposure of the general population to hydrogen sulfide emanating from a specific source have been investigated and described. For the most part, these events involved only annoyance because of the odour or, at worst, minor temporary illness such as headache, nausea, and sleeplessness. However, as described in section 6.3, on two occasions, general population exposure to hydrogen sulfide caused grave illness and even death: one at Poza Rica, Mexico, and the other in and around Rotorua, New Zealand.

Unfortunately, these incidents were not studied using epidemiological techniques, and it is not possible to establish exposure-effect relationships from the data.

### 7.5 Guidelines for the Protection of Public Health

There are two aspects concerning the protection of public health in relation to hydrogen sulfide exposure: *(a)* the protection of the public, and occupational groups in particular, from the toxicological effects of such exposure; and *(b)* the protection of the public from

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The odour threshold for hydrogen sulfide has been variously reported to range from 0.0007 mg to 0.20 mg/m³ (0.0005–0.13 ppm) (Table 2). Little information is available on the odour detection limits for ambient hydrogen sulfide either under experimental field conditions or in general population exposures. The Task Group considered that a level of 0.007 mg/m³ (0.005 ppm) averaged over 30 min should not produce odour nuisance in most situations. Some regulatory bodies may wish to adopt longer averaging times with appropriately adjusted concentration limits.

The best estimates available suggest that eye irritation may occur in man after several hours' exposure to hydrogen sulfide concentrations of 16–32 mg/m³ (10.5–21.0 ppm). As occupational exposure guidelines, the Task Group recommended the adoption of 10 mg/m³ (7 ppm) as a workshift time-weighted average value together with a short-term exposure limit of 15 mg/m³ (10 ppm). The short-term limit should be determined as a 10-min or less averaged value. These limits should prevent eye irritation in workers which represents the earliest recognized toxic response in man.

Annex tables 1 and 2 contain various national standards or recommendations for ambient air quality and occupational exposure limits for hydrogen sulfide. As can be seen, there is considerable consensus regarding occupational exposure limits and the recommendations of the Task Group are generally consistent with the national values. There is less agreement regarding ambient air quality standards, possibly because of different values placed on the nuisance value of odours.

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## Annex

Annex table 1. Ambient air quality standards for hydrogen sulfide from selected countries

| Country | Long-term | | | Short-term | | | Reference |
|---|---|---|---|---|---|---|---|
| | mg/m³ | ppm | averaging time (h) | mg/m³ | ppm | averaging time (min) | |
| Bulgaria | 0.008 | 0.006 | 24 | 0.008 | 0.006 | 30 | Newill (1977) |
| China | — | — | — | 0.01 | 0.007 | 20 | Official Communication[d] |
| Czechoslovakia | 0.008 | 0.006 | 24 | 0.008 | 0.006 | 30 | Newill (1977) |
| German Democratic Republic | 0.008 | 0.006 | 24 | 0.015 | 0.011 | 10—30 | Newill (1977) |
| Germany, Federal Republic of | 0.005 | 0.004 | 24 | 0.01 | 0.007 | 30 | Federal Minister for Home Affairs (1974) |
| Hungary | 0.008[a] | 0.006 | 24 | 0.008[a] | 0.006 | 30 | Newill (1977) |
| Hungary | 0.15 | 0.11 | 24 | 0.3 | 0.21 | 30 | Newill (1977) |
| Israel | 0.045 | 0.032 | 24 | 0.15 | 0.11 | 30 | Newill (1977) |
| Philippines | — | — | — | 0.3 | 0.21 | 30 | UNEP/IRPTC[e] |
| Poland | 0.008[b] | 0.006 | 24 | 0.008[b] | 0.006 | 30 | UNEP/IRPTC[e] |
| Poland | 0.02[c] | 0.014 | 24 | 0.06[c] | 0.04 | 20 | UNEP/IRPTC[e] |
| Romania | 0.01 | 0.007 | 24 | 0.03 | 0.02 | 30 | Newill (1977) |
| Spain | 0.004 | 0.003 | 24 | 0.01 | 0.007 | 30 | Newill (1977) |
| USSR | 0.008 | 0.006 | 24 | 0.008 | 0.006 | 30 | Newill (1977) |
| Yugoslavia | 0.008 | 0.006 | 24 | 0.008 | 0.006 | 30 | Newill (1977) |

[a] For highly protected and protected areas.
[b] For especially protected areas, sanatoria, health resorts, sanctuaries, and national parks.
[c] For protected areas, towns, and villages.
[d] Official communication from the Institute of Health, Chinese Academy of Medical Sciences.
[e] Private communication.

### Note by the WHO Task Group

Ambient Air Quality Standards have been set according to different criteria in different countries, and these criteria may include, but are not necessarily limited to the assessment of health effects. Moreover, the limits themselves may have different meanings such as the maximum acceptable level or the permissible level over a 10 to 30-min averaging time, etc.

Annex table 2. Occupational exposure standards for hydrogen sulfide from selected countries[a]

| Country | mg/m³ | ppm | Standard type |
|---|---|---|---|
| Australia | 15 | 10 | 8-h TWA[b] |
| Belgium | 15 | 10 | 8-h TWA[b] |
| Bulgaria | 10 | | ceiling |
| China | 10 | | ceiling |
| Czechoslovakia — average | 10 | | shift[c] TWA[b] |
| maximum | 20 | | 10-min STEL[d] |
| Finland | 15 | 10 | 8-h TWA[b] |
| German Democratic Republic — average | 15 | | 8.75-h TWA[b] |
| short-term | 15 | | 30-min STEL[d] |
| Germany, Federal Republic of | 15 | 10 | 8-h TWA[b] |
| Hungary | 10 | | 8-h TWA[b] |
| Italy | 10 | | shift[c] TWA[b] |
| Japan | 15 | 10 | shift[c] TWA[b] |
| Netherlands | 15 | 10 | shift[c] TWA[b] |
| Poland | 10 | | 8-h TWA[b] |
| Romania — average | 10 | | shiftTWA[b] |
| maximum | 15 | | ceiling |
| Sweden | 15 | 10 | shift[c] TWA[b] |
| Switzerland | 15 | 10 | 8 to 9-h TWA[b] |
| USSR | 10 | | less than 30-min STEL[d] |
| USA — occupational standard | | 20 | ceiling except for one 10-min peak less than 50 ppm |
| ACGIH | 15 | 10 | 8-h TWA[b] |
| Yugoslavia | 21 | 15 | 15-min STEL[d] |
| | 10 | 7 | ceiling |

[a] Abstracted from: ILO (1977).
[b] TWA = time-weighted average value.
[c] = a time-weighted value averaged over the entire shift or workday.
[d] STEL = short-term exposure limit.